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Mechanisms and Properties of Long-Term Synaptic Plasticity in the Brain: Relationships to Learning & Memory

A. Hashemi-Sakhtsari

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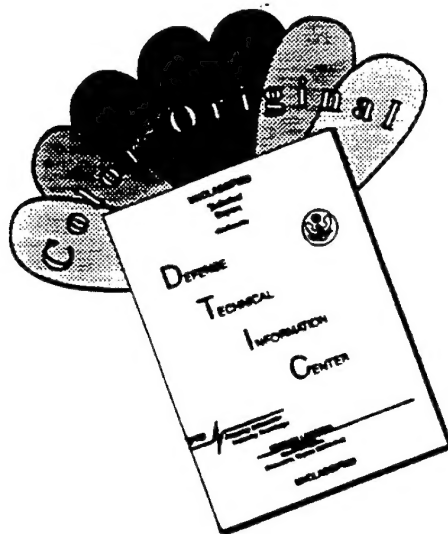
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# Mechanisms and Properties of Long-Term Synaptic Plasticity in the Brain: Relationships to Learning and Memory

*A. Hashemi-Sakhtsari*

Information Technology Division  
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DSTO-TR-0345

## ABSTRACT

Functional and structural changes in synapses, specific regions for communication between nerve cells, are thought to be the basis for storing information, and modulating neuronal behaviour. This continuous remodelling is defined as synaptic plasticity. The process of learning involves stable changes in synaptic efficacy. Long-term potentiation in the hippocampus and long-term depression in the cerebellum are two forms of long-lasting synaptic plasticity that currently serve as our primary experimental models of learning and memory formation. In recent years, there have been considerable advances in understanding the cellular and molecular mechanisms of these forms of synaptic plasticity. This report presents an overview of these developments, considers the relationship of long-term synaptic plasticity mechanisms to learning and memory in view of these developments, and suggests future directions for research in this rapidly growing area of neuroscience. Amongst these proposals, any artificial neuronal network model should contain elements that imitate the use-dependent increase (or decrease) of synaptic efficiency.

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# Mechanisms and Properties of Long-Term Synaptic Plasticity in the Brain: Relationships to Learning and Memory

## EXECUTIVE SUMMARY

Plasticity is the tendency of synapses and neural circuits to change as a result of activity. There are various ways in which synaptic efficacy might be altered; for example, transmitter release, or the responsiveness of the postsynaptic cell can be enhanced. Most of the research revolves around the hippocampus and the cerebellum, two areas of the brain with well defined circuitry. This review therefore focuses on recent studies of two major forms of plasticity studied in these structures: Long-term potentiation (LTP) in the hippocampus, and long-term depression (LTD) in the cerebellum.

In 1973, Lømo, Bliss and Gardner-Medwin, from Per Andersen's laboratory in Oslo, found that a sustained volley of impulses (100 Hz for about 1 sec) along the input perforant path fibres entering the dentate gyrus of the rabbit hippocampus resulted in a dramatic and long-lasting increase in the strength of excitatory transmission at the synapses on granule cells. They called this effect *long-term potentiation*, which has become accepted as a model of learning and memory.

In the hippocampus, LTP is expressed as a persistent and synapse-specific increase in the amplitude of synaptic responses elicited by low-frequency stimulation of the excitatory afferents, which release glutamate across their synapses. This excitatory transmitter stimulates two sub-classes of glutamate receptor. These are called ionotropic, and metabotropic receptors (mGluRs). The ionotropic receptors, designated NMDA and non-NMDA receptors, alter membrane permeability to ions, leading to excitatory depolarisation which triggers postsynaptic discharges. The mGluRs are non-NMDA and activate intracellular messengers. Once NMDA receptors open, there is an influx of calcium ( $\text{Ca}^{2+}$ ) into the cell which, together with activation of the mGluRs, sparks off a cascade of biochemical changes that bring about LTP. Importantly, one of these is a retrograde message that enhances the transmitter release induced by a single unit discharge in the presynaptic ending. Thus these NMDA receptors perhaps lie at the molecular heart of memory. Manipulations that prevent NMDA receptor activation, or the responses they induce such as postsynaptic hyperpolarisation, or application of NMDA receptor antagonists, as well as intracellular injection of  $\text{Ca}^{2+}$  chelators, all prevent LTP initiation.

LTP as a process can be broken down into 3 conceptual components: changes that lead to its *induction*, *maintenance* and *expression*. Of these, the *induction* of LTP depends on postsynaptic depolarisation, leading to the inrush of  $\text{Ca}^{2+}$  and the

subsequent activation of second messenger kinases that modify intracellular metabolism, whereas the *maintenance* and *expression* of LTP depend on postsynaptic changes, although an enhancement of glutamate release from the presynaptic terminal likely to also be involved. The latter mechanism implies retrograde diffusion of a messenger, probably nitric oxide, from the postsynaptic cell. This notion of retrograde transport provides an entirely new principle of cell communication that likely needs to be incorporated into artificial neuronal network models.

Once LTP has been triggered, it can last for hours to several weeks *in vivo*, enduring enough to make it a likely candidate for the physical changes that underpin the formation of recent memories. There are other main reasons why LTP has become so central to theories about learning: Firstly, it acts in an impeccably "Hebbian" manner, only taking place at pre- and postsynaptic synapses connecting neurones that are both active at the same time (Donald Hebb proposed such a learning relationship in 1949). This is pairing presynaptic activity with postsynaptic depolarisation. Secondly, it behaves like a cellular mimic of classical (Pavlovian) conditioning. Synaptic activity in a "weak" afferent pathway that is unable to support LTP can be made to do so if paired (associated) with synaptic activity in a "strong" pathway that is able to produce LTP independently. Thirdly, there is a high correspondence between optimal LTP induction conditions and endogenous patterns of neural activity in the theta range of 4-12 Hz that accompany learning. GABA is the major inhibitory neurotransmitter in the brain. Theta frequency activity facilitates GABA<sub>B</sub> autoreceptor-mediated depression of inhibitory interneurons, thereby opening a time window for the postsynaptic target to sufficiently depolarise and activate NMDA receptors. Further strong support for a role of LTP in memory is provided by the observation that the animal fails to learn new tasks when NMDA or AMPA sub-types of glutamate receptors in the hippocampus are blocked by selective antagonists. Also, prior to stabilisation, LTP formation can be disrupted by a variety of manipulations such as hypoxia, electroconvulsive shock or seizure activity, trains of low frequency stimuli, and cooling. Such vulnerability of LTP to disruption suggests a possible basis for the consolidation period frequently observed in behavioural studies of learning and memory.

If LTP is a mechanism for strengthening connections between synapses, then to avoid synaptic saturation, a complimentary prolonged inhibiting mechanism probably exists to *decrease* synaptic strength. One mechanism that has recently received much attention is associative *long-term depression* (LTD) of synaptic transmission. LTD provides a means of regulating the strength of synaptic connections in the mammalian brain. It has been most thoroughly studied in the mammalian cerebellum at the parallel fibre-Purkinje cell synapse by Ito and his colleagues.

LTD in the cerebellar cortex can be induced either by pairing low-frequency activity (1-4 Hz) in parallel fibres (PFs) and climbing fibres (CFs), two excitatory afferent pathways that converge on cerebellar cortical Purkinje cells, or by pairing PF activity with direct Purkinje cell hyperpolarisation. As in the hippocampus, fast excitatory synaptic transmission at both PF and CF synapses is mediated primarily by postsynaptic AMPA receptors. However unlike LTP induction, the critical events in LTD induction involve the coupling of a potent Ca<sup>2+</sup> signal generated by CF discharge with activation of mGluRs at parallel fibre-Purkinje cell synapses.

Although an increase in intracellular  $\text{Ca}^{2+}$  in postsynaptic Purkinje cells is required for cerebellar LTD, this does not involve NMDA receptors.

Cerebellar LTD is long-lasting. It obeys Hebbian rules, and the Hebbian nature of cerebellar LTD also provides for associativity. Also, as noted, LTD is specific to stimulated synapses.

It is generally agreed that the common biochemical pathway for the induction and expression of both hippocampal LTP and cerebellar LTD is an elevation of intracellular  $\text{Ca}^{2+}$ , an activation of enzymatic cascades, and a modification of postsynaptic AMPA and metabotropic sub-types of glutamate receptors.

Storage of initial information, a type of short term memory, lasts minutes to hours and involves changes in the strength of existing synaptic connections by protein phosphorylation (through second messenger-mediated modifications by kinases). The long term changes that persist for weeks and months are stored at the same site, but may involve activation of genes, with the subsequent expression of new proteins, and growth of new connections, including an increase in the number of presynaptic terminals. A recently discovered family of genes, called *immediate early genes* (IEGs), are not normally active, but rapidly become activated by brief bursts of action potentials. As master switches initiating long term changes in the brain, IEGs encode transcription factors, proteins that regulate the expression of other genes. There is evidence that impulse activity increases the expression of genes that encode trophic factors, which are proteins that promote the survival of neurones.

Artificial neuronal networks with plasticity rules derived from hippocampal LTP have been shown to have a very large storage capacity and be able to produce an optimal classification of input signals. Similarly, artificial networks designed according to cerebellar cortex circuitry exhibit properties of complex motor learning and adaptation.



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## Foreword

Defence research programmes overseas are incorporating neurophysiological mechanisms and properties into system architectures in order to overcome limitations of current information technology. Exploiting the unique mechanisms present in natural neuronal networks and applying these to information processing architectures and algorithms provides systems which are intelligent and adaptive, thus facilitating command, control and intelligence organisation, and human performance evaluation and cognitive modelling. The US Defence Advance Research Projects Agency (DARPA) has a considerable programme to investigate the advantages offered by cognitive and neuroscience research.

This technical report is aimed at introducing some of the relevant concepts related to the way neurones communicate, and their activity-dependent structural modification that may well produce significant benefits to future systems. Areas such as machine learning, memory management, speed of recall from databases, and dealing with complex queries could benefit.

This review paper explores neurophysiological mechanisms and components which support forms of knowledge and skill acquisition, retention and expression, as well as sensing and pattern recognition. The development of artificial neural mechanisms based on these biological features and properties is an important area in future research and development. Artificial neuronal networks with enhanced classification and pattern matching performance, larger storage capacity, and better adaptation "skills" are being developed. It is suggested that such work needs to be pursued in order to provide and maintain a leading edge in defence capability.



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## **Receptor Mechanisms - Definition of Some Common Terms**

**Ion Channel** - A protein that can form an aqueous pore through which ions cross the cell membrane. This flow of ions determines cell excitability and its firing properties, the main ions being sodium, potassium, calcium and chloride.

**Receptor** - A protein molecule which is capable of selectively binding a drug, hormone or neurotransmitter, thereby eliciting a physiological response. Transmitter receptors can be grouped into two superfamilies. One family consists of ion channels which produce fast synaptic transmission lasting for milliseconds. The other group does not form channels. Instead these receptors are indirectly linked to their effectors, including channels, through guanosine 5'-triphosphate (GTP)-binding proteins (G-proteins), and have a modulatory role. The G-protein linked biochemical effects are slow in onset, and they last longer than the directly gated receptor responses.

**Ligand** - Any substance that binds to a particular type of receptor.

**Agonist** - A drug, hormone or transmitter substance that elicits a cellular response when it combines with its receptors.

**Antagonist** - A drug that binds to receptors without itself producing a biological response but that, rather, decreases the effect of agonists.



# 1. Introduction

Learning is acquisition of new information, a new skill or a new behaviour pattern. Memory is storage (consolidation) of what has been learnt, maintenance, or remembering (retrieval) of what has been stored. Memory allows us to cope with environmental demands, adapting to changes in conditions of life. It also allows us to modify our behaviour by experience.

Different regions of brain are believed to be involved in storing memories. These are prefrontal cortex (Artola and Singer, 1993), temporal lobes, in particular the hippocampus (Zola-Morgan and Squire, 1990), and the cerebellum (Thompson, 1990). Figure 1 shows various brain structures associated with memory.

The role of temporal lobes, particularly the hippocampus, in memory was established during 1940s and 50s. Wilder G Penfield, a neuro-surgeon at the Montreal Neurological Institute, began to use electrical stimulation to map motor, sensory and language functions in the cortex of more than 1000 patients undergoing neurosurgery for the relief of epilepsy. During these explorations, memory-like responses were elicited from the temporal lobes. Additional evidence came in the 1950s from the study of a few patients who underwent bilateral removal of the hippocampus and neighbouring regions in the temporal lobe as treatment for epilepsy. In the first and best-studied case, described by Brenda Milner of the Montreal Neurological Institute (Scoville and Milner, 1957; Milner, 1966), the patient had lost the capacity to form new long-term memories. This patient had an intact

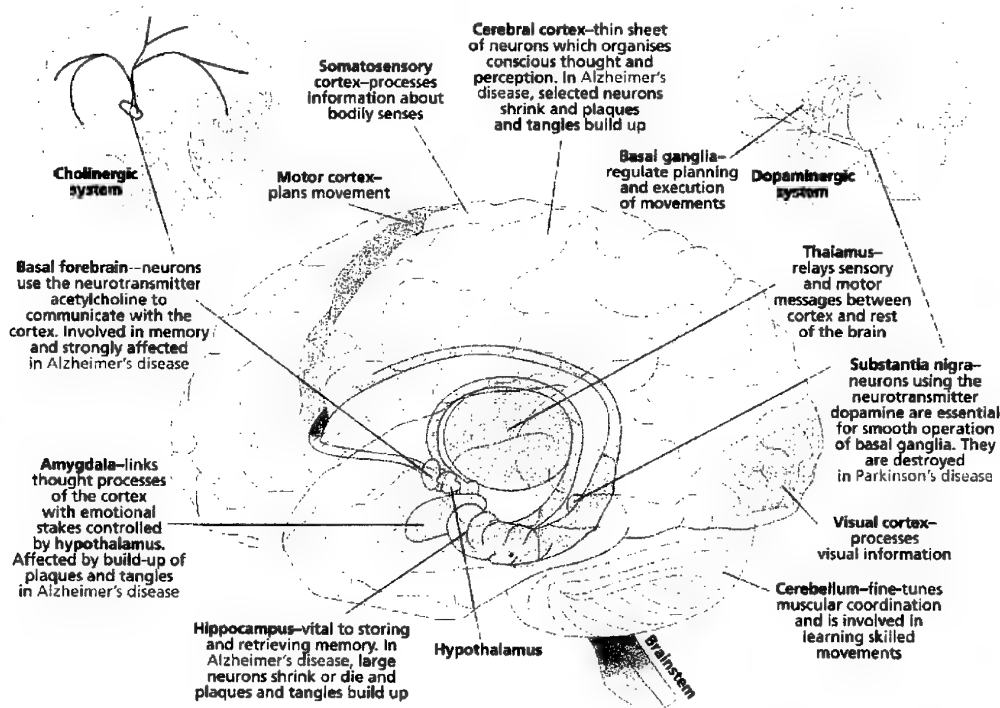


Figure 1. Many structures in the brain are involved in learning and memory. Particular attention has however been paid to Hippocampus and cerebellum.



short-term memory, but lacked the ability to translate what he learned from short-term to long-term memory. For example, he could converse normally with the hospital staff, but could not remember them even though he saw them every day.

Researchers agree that lesions of the temporal lobes severely impair forms of learning and memory that require a conscious record. These types of learning are commonly called “declarative” or *explicit*. Those forms of learning that do not utilise conscious participation remain surprisingly intact in patients with temporal lobe lesions; they are referred to as “procedural”, non-declarative or *implicit* (Kandel and Hawkins, 1992).

Explicit learning is fast and may take place after only one training trial, so called “one-shot” learning. It often involves association of simultaneous stimuli and permits storage of information about a single event that happens in a particular time and place; it therefore affords a sense of familiarity about previous events, as it can be brought to mind and be reflected upon. In contrast, implicit learning is slow and accumulates through repetition over many trials. It often involves association of sequential stimuli and permits storage of information about predictive relations between events. Implicit learning is expressed primarily by improved performance of certain tasks without the subject being able to describe just what has been learned, and it involves memory systems that do not draw on the contents of the general knowledge of the individual. In the case of implicit learning, experience alters behaviour nonconsciously. Implicit learning is thought to be expressed through activation of the particular sensory and motor systems engaged by the learning task; it is acquired and retained by the plasticity inherent in these neuronal systems. As a result, implicit learning can be studied in various reflex systems in either vertebrates or invertebrates. Indeed, even simple invertebrate animals show excellent reflexive learning (Kandel and Hawkins, 1992; Young and Concar, 1992).

### 1.1. Steps in processing memories

There are three steps involved in processing memories:

- Immediate Memory* - This memory is labile. It only lasts for a short time when attention is being paid to a task.
- Short-term memory* - Consolidation of meaningful events occurs during this period. This memory is still vulnerable, and may equate with “working memories” retrieved from store. During this phase current sensory data is compared with stored knowledge, allowing sequential planning for the next contingency. As will be discussed in depth, it is believed that short term memories involve temporary facilitation of passage of information through the synapse, perhaps by the release of more *neurotransmitter*.
- Long-term memory* - It is presumed that remote long-lasting memories require permanent modification of synaptic structures. Such memories are retained despite periods of unconsciousness, hypothermia, etc. These demand a large storage capacity, so it takes time to recall them. A delay in cueing is a common

experience. The problem of recall (the memory of a memory that can be activated) remains a crucial problem.

Conversion of short term memory to long term stores depends on (i) the state of arousal and (ii) the number of repetitions. Perhaps each time a signal passes it makes it easier for subsequent similar signals to overcome synaptic "resistance". It is yet to be demonstrated that learning may involve reverberating circuits. The primary role of the hippocampus appears to be to consolidate new associations for days to weeks. Although hippocampus helps us to form new memories, it can not be the final storage site, for many old memories survive its destruction. Judging from studies of patients with amnesia, older memories are stored in the cortex, and not the hippocampus. However, the neural architecture of the temporal lobe indicate that the hippocampus and cortex engage in an intense dialogue. For a recent reference on time-limited role of hippocampus in memory storage see Zola-Morgan and Squire (1990).

## 1.2. Working memory

The combination of moment-to-moment awareness and instant retrieval of archived information constitutes working memory. Working memory enables us to hold fleeting material in our heads so that we can build and understand complex sentences. This type of memory would come into play if, for example, one was to read off a serial number in order to write it down. Lines of evidence indicate that the operations of working memory are carried out in a part of the brain known as the prefrontal lobes of the cerebral cortex (Goldman-Rakic, 1992). The prefrontal cortex is necessary for retrieving the products of such associative learning from long-term storage elsewhere in the brain for use in the task at hand.

It is proposed that there are multiple memory systems in the brain (Squire, 1992; Macdonald and White, 1993), and that, in particular, prefrontal cortex is divided into multiple domains, each specialised for encoding a different kind of information, such as the location of objects, the feature of objects and, additionally in human, semantic and mathematical knowledge (Funahashi et al., 1989; Goldman-Rakic, 1992). Indeed, it is interesting to note that brain seems to hold visual information received in the form of words and pictures in different areas of the temporal lobe (see Young and Concar, 1992), and recalling or thinking about particular images activates those same areas.

## 2. Functional Anatomy of Neurones

The basic unit of the nervous system is the individual nerve cell, or neuron. However, only about 10 percent of the cells in the nervous system are neurones, the remainder are glial cells, which probably metabolically sustain the neurones and physically support them.

As shown in figure 2, the neuron can be divided structurally into 3 parts, each associated with a particular function: (1) the *dendrites* and *cell body*, (2) the *axon*, and (3) the *axon terminals*. The dendrites form a series of highly branched cell outgrowths (some 10-100 per neuron) as extensions of the cell membrane of the neuron cell body. The dendrites and cell body are the site of most of the specialised junctions with other neurones through which signals are passed to the cell. The axon, or nerve fibre, is a single long process extending from the cell body, usually considerably longer than dendrites. The axon can give off branches called collaterals along its course, and near the end it undergoes considerable branching into numerous axon terminals. The last part of axon terminal is enlarged and is responsible for transmitting a signal from the neuron to the cell it contacts.

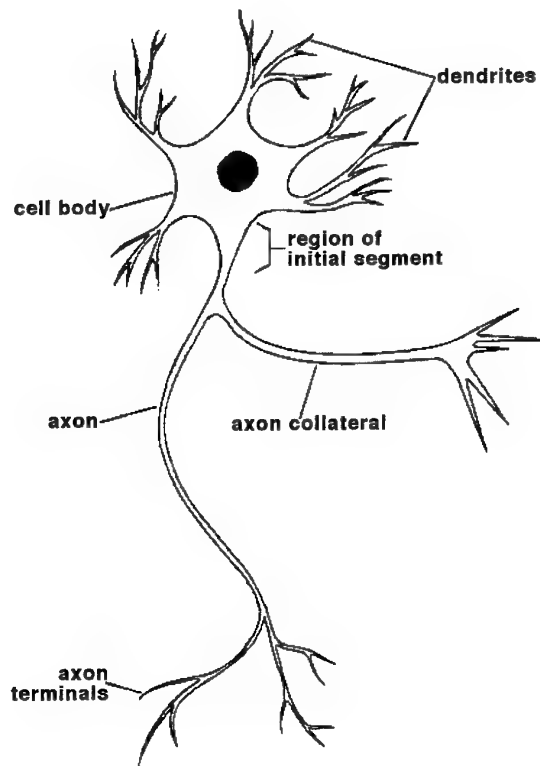


Figure 2. Diagrammatic representation of a neuron.

Neurones assume many different shapes, depending on their role and sometimes the axon and dendrites are hard to distinguish. Figure 3 shows three types of neurones found in the hippocampus and cerebellum.

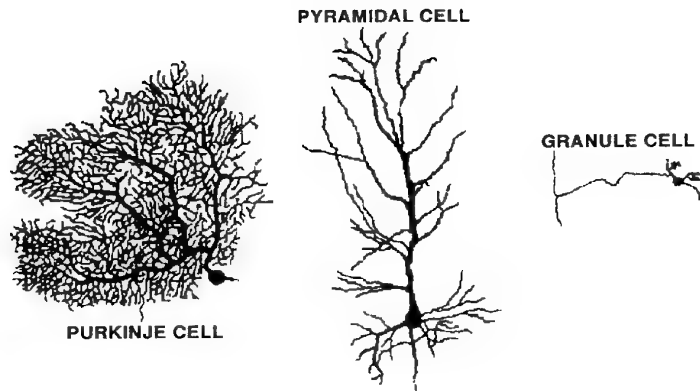


Figure 3. Structural variety of neurones, shown as tracings from Golgi stains, contributes to the vast capacity of the brain to store, retrieve, use and express information as well as to experience emotion, and control movement.

In most cells, the threshold of the *initial segment*, as shown in figure 2, is lower than that of their dendrites and cell body. The initial segment is activated first. The action potential generated in the initial segment then propagates both down the axon and back over the cell body. Synapses next to the initial segment have a greater influence on cell activity than those at the end of the dendrites, and thus synaptic placement provides a mechanism for giving different inputs varying influence on the output of a post-synaptic cell.

Neurones are divided into 3 classes: *afferent* neurones, *efferent* neurones and *interneurones*. The afferent neurones carry information from the periphery to the central nervous system (CNS). Efferent neurones transmit the final integrated information from the CNS to the effector organs. Those efferent neurones which innervate skeletal muscle are called motor neurones. The third group of nerve cells, the interneurones, both originate and terminate within the CNS, and 99% of all nerve cells belong to this group. The interneurones and their connections, in large part, account for learning and memory.

### 3. Neuronal Communication

A neuron that has been excited conveys information to other neurones by generating impulses known as *action potentials*. These signals propagate like waves down the length of the cell's single axon and are converted to chemical signals at *synapses*.

The sodium concentration in the extracellular space is about 10 times the intracellular concentration. When a neuron is at rest, its external membrane maintains an electrical potential difference of about -70 mV (the inner surface is negative relative to the outer surface). At rest, the membrane is 50 to 75 times more permeable to potassium ions than to sodium ions, and it is these potassium ions rather than sodium ions that govern the resting potential. When the cell is stimulated to decrease the voltage gradient, or to depolarise the membrane, the permeability to sodium increases, leading to an inrush of positive charges. This inrush triggers an impulse, a momentary reversal of the membrane potential. The rising phase is called *depolarisation*. After about 1 ms the sodium permeability declines, and the membrane potential returns to -70 mV. Potassium conductance is increased during this *repolarisation* phase. The impulse is initiated at the junction of cell body and the axon and is conducted away from the cell body. The action potential measures about 100 mV in amplitude and 1 ms in duration. Figure 4 shows an action potential. The sodium permeability mechanism remains refractory for a few milliseconds after each explosion. This limits to 200 or less per second the rate at which action potentials can be generated.

Axons are not good conductors as the resistance along the axis is high and the membrane resistance is low. The positive charge that enters the axon during the action potential is dissipated in 1 or 2 mm. In order to travel distances that may reach centimetres, the action potential must be frequently regenerated along the way. This limits the maximum speed at which an impulse travels to about 100 meters per second. Thus, action potentials are relatively low frequency, stereotypical signals that are conducted at a snail's pace. Fleeting thoughts must depend on the relative timing of impulses conducted over many axons in parallel, and on thousands of connections made by each one.

Some neurones such as the pyramidal cells in the hippocampus have dendritic membrane containing voltage-dependent  $\text{Ca}^{2+}$  channels. This means that when depolarisation in the dendrite reaches a certain threshold, these channels open, permitting  $\text{Ca}^{2+}$  to flood into the cell. The rise in  $\text{Ca}^{2+}$  concentration causes further depolarisation and the opening of other voltage-dependent  $\text{Ca}^{2+}$  channels in neighbouring dendritic membranes. Under such conditions, a spike is produced in the dendrite. Therefore, dendrites are semi-independent processing units that can "make decisions", suggesting that under some circumstances the "unit" of processing may really be the dendritic branch (Churchland and Sejnowski, 1992).

#### 3.1. A synapse

A synapse is an anatomically specialised junction between two neurones where the electric activity in one neuron influences the excitability of the second (see figure 4). The human brain has about 100 billion neurones and 100,000 billion synapses. If, as neuroscientists believe, learning results from small adjustments to the strengths of these synapses, then the origin of the brain immense capacity is clear. Even storing

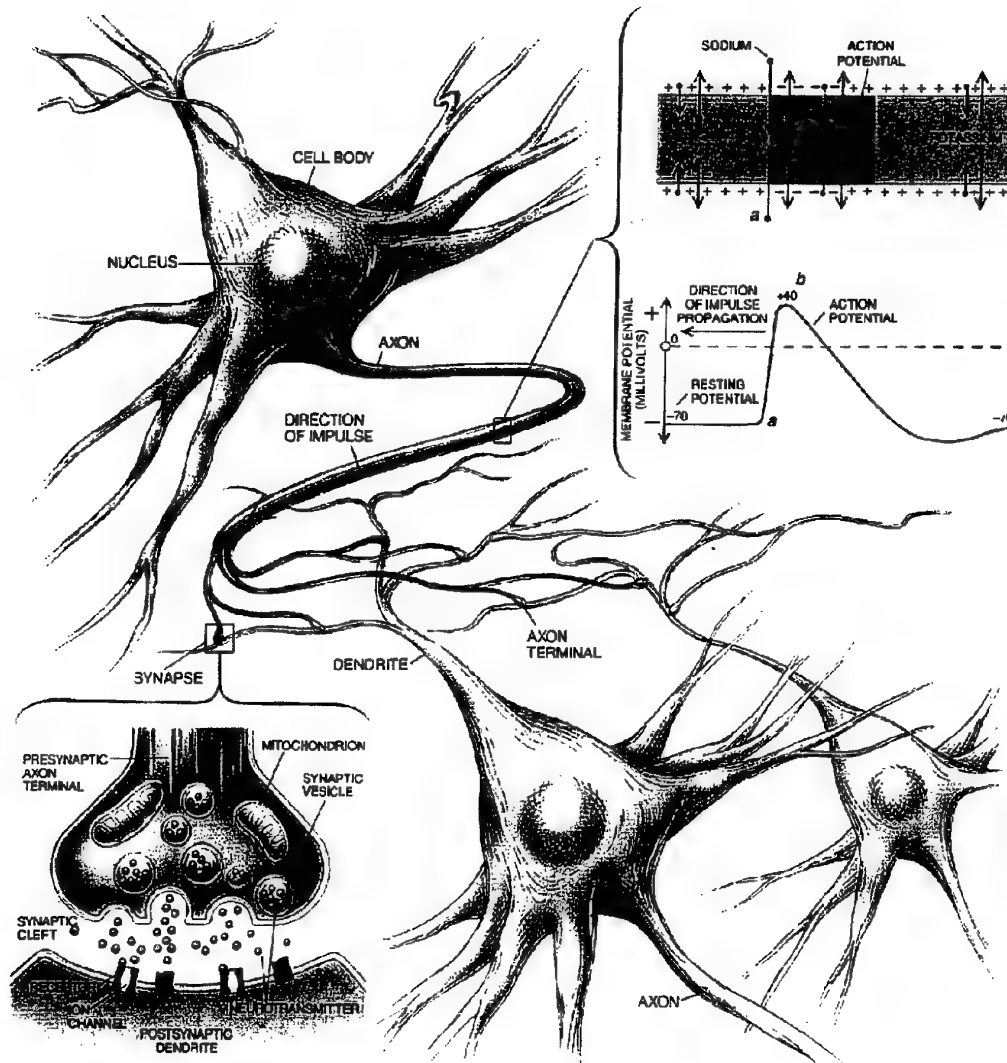


Figure 4. Characteristics of an action potential and direction of travel of the depolarising impulse along the nerve cell axon.

information at the low average rate of one bit per synapse, which would only require two levels of synaptic activity (high and low), the structure as a whole would generate  $10^{14}$  bits.

Most synapses occur between the axon terminals of one neuron and the cell body or dendrites of a second. The neurones conducting information towards synapses are called *presynaptic* neurones, and those conducting information away are *postsynaptic* neurones. Figure 5 shows how in a multi-neuronal pathway, a single neuron can be postsynaptic to one group of cells and, at the same time, presynaptic to another.

Every postsynaptic neuron has thousands of synaptic junctions on the surface of its dendrites or cell body. The level of excitability of this cell depends on the number of

synapses active at any one time, and how many are excitatory or inhibitory. In this manner, postsynaptic neurones function as neural integrators, i.e. their output reflects the sum of all the incoming bits of information arriving in the form of excitatory and inhibitory synaptic inputs.

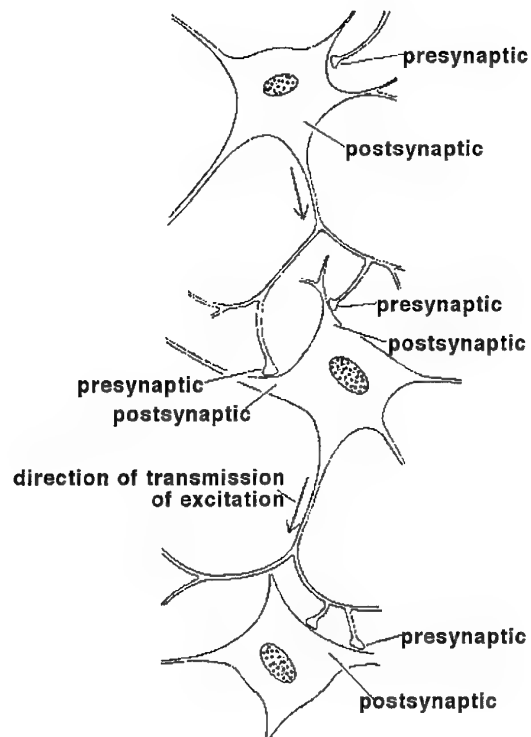


Figure 5. Diagrammatic representation of connections between pre- and post-synaptic neurones.

## 4. Synaptic Transmission

This is the transfer of signal from one cell to another. Two distinct modes of transmission are known, one electrical and the other chemical.

### 4.1. Transmission at electrical synapses

At electrical synapses, currents generated by an impulse in the presynaptic nerve terminal spread directly to the next neuron through a low-resistance pathway. The sites for electrical communication between cells have been identified in electron micrograph as *gap junctions*, in which the usual intercellular space of several tens of nanometer is reduced to about 2 nm. Pairs of particles, each made of protein sub-units, span the gap junction. The unit constituted by a particle pair has been termed a *connexon*. Most electrical synapses do not exhibit rectification, but conduct equally well in both directions. One advantage of an electrical synapse is the absence of the synaptic delay of 0.5 to 1 ms associated with chemical synaptic transmission. Electrical coupling can also produce sub-threshold or integrative actions between nerve cells. Multiple electrical synapses converging on a neuron have simple additive effects with little fluctuation.

Surprisingly, in addition to producing excitation, current flow between cells is known to produce inhibition at a specialised site.

Electrical synapses are not studied in this report.

### 4.2. Transmission at chemical synapses

At chemical synapses, the axon terminal of the presynaptic neuron ends in a slight swelling, the *synaptic knob* (*synaptic bouton*). A narrow (20 nm) extracellular space, the *synaptic cleft*, separating the pre- and post-synaptic neurones prevents direct propagation of the action potential from the presynaptic neuron to the postsynaptic cell. Information is transmitted across the synaptic cleft by means of a chemical agent stored in small, membrane-enclosed vesicles in the synaptic knob. When an action potential in the presynaptic neuron reaches the axon terminal and depolarises the synaptic knob, small quantities of the chemical transmitter are released from the synaptic knob into synaptic cleft. Neurotransmitters are released in small, uniformly sized packets, with each nerve impulse prompting the discharge of a large number of packets. During the peak of the action potential (neuronal depolarisation),  $\text{Ca}^{2+}$  enters the terminals through voltage-regulated  $\text{Ca}^{2+}$  channels.  $\text{Ca}^{2+}$  triggers and coordinates neurotransmitter release. Immediately after this neuronal activity, the intracellular  $\text{Ca}^{2+}$  is rapidly buffered, sequestered and extruded. There are about 5000 transmitter molecules per vesicle at central synapses. Once released from the vesicles, the transmitter diffuses across the synaptic cleft and combines with receptor sites on the postsynaptic cell membrane lying under the synaptic knob, referred to as *subs synaptic membrane* (figure 6).

The combination of the transmitter with the receptor sites causes ion channels to open, changing the permeability of the subsynaptic membrane and hence the membrane potential of the postsynaptic cell, leading to the generation of action potential in the postsynaptic neuron. There is a synaptic delay of less than 1 ms between excitation of pre-synaptic terminal and membrane potential changes in the



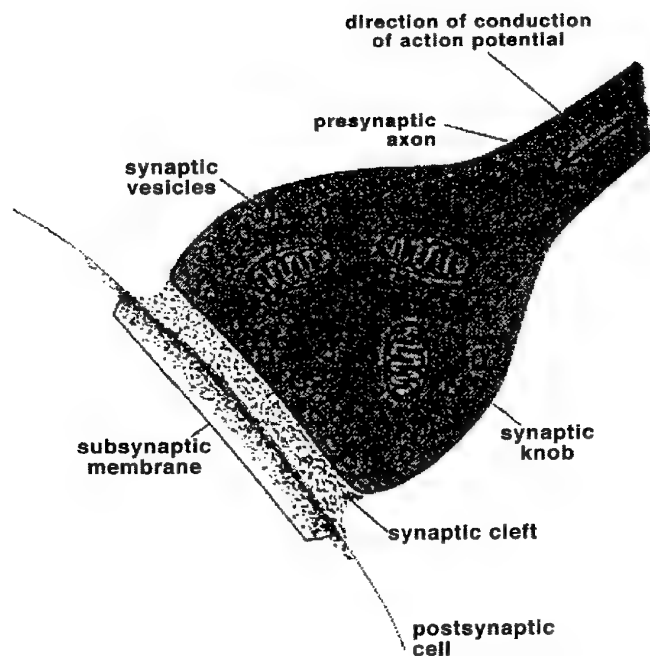


Figure 6. A chemical synapse.

postsynaptic cell. Chemical synapses provide a very large amplification mechanism. Synaptic activity is terminated when the transmitter is chemically transformed into an ineffective substance, simply diffuses away from the receptor sites, or is taken back by the synaptic knob. Figure 7 shows transmission across chemical synapses. When two neurones are electrically active at the same time (A), their synapses may grow more efficient such that the postsynaptic neuron fires more readily than usual (B) in response to excitatory signals from the presynaptic neuron.

A third type of synapse in which electrical and chemical synaptic transmission are combined is also known. Perhaps, more frequently, postsynaptic cells receive chemical and electrical synaptic inputs and integrate them.

#### 4.2.1. Excitatory synapses

An excitatory synapse, when activated, increases the likelihood that the membrane potential will reach threshold and the cell will undergo an action potential. Here the permeability of the subsynaptic membrane to positively charged ions is increased. At the subsynaptic membrane of excitatory synapses there occurs the simultaneous movement of a small number of potassium ions out of the cell and a large number of sodium ions (and a small amount of calcium ions) into the cell. The net movement of positive ions is into the neuron, which slightly depolarises the postsynaptic cell. This potential change, called the *excitatory postsynaptic potential* (EPSP), is a local, passively propagated potential (figure 8); its only function is to help trigger an action potential.

A single EPSP in a motor neuron is estimated to be only 0.5 mV whereas changes up to 25 mV are necessary to depolarise the membrane from its resting level to threshold. To set the intensity of its output, each neuron must continually integrate

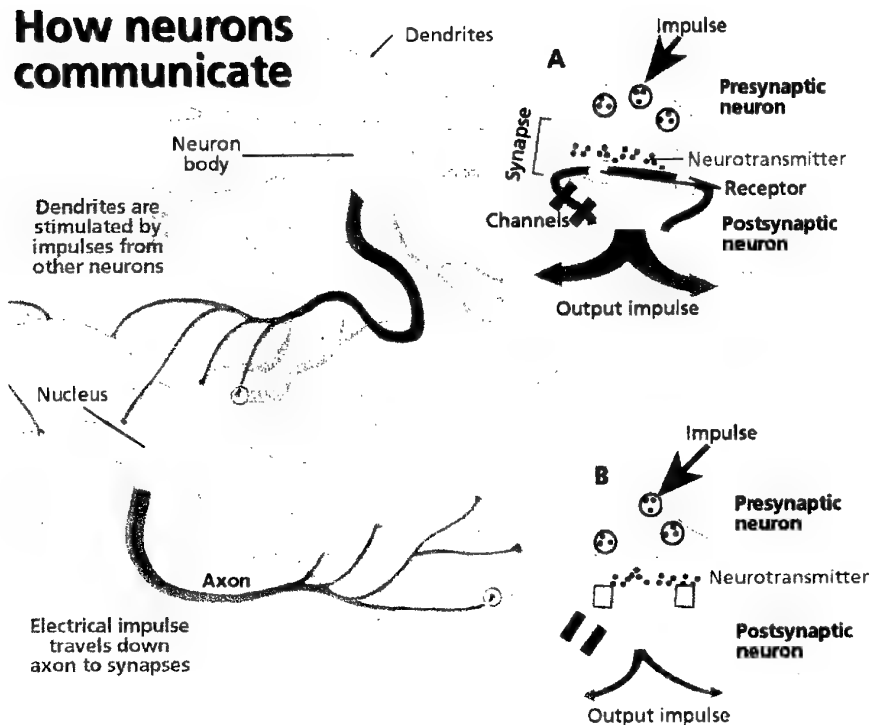


Figure 7. A simplified diagram showing neuronal communication, and generation of impulses in postsynaptic neurones.

up to 1000 synaptic inputs. These inputs do not add up in a simple linear manner. Each neuron is a sophisticated computer.

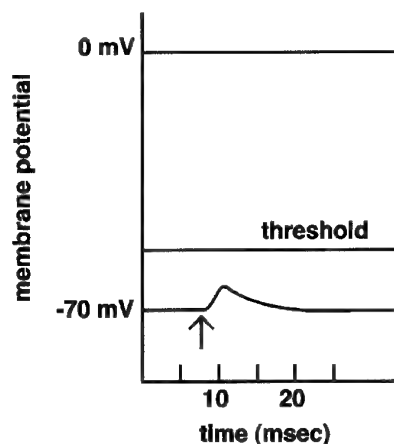


Figure 8. Excitatory postsynaptic potential (EPSP). Stimulation of the presynaptic neuron is marked by the arrow. Note the short synaptic delay before the postsynaptic cell responds.

There is a general depolarisation of the membrane towards threshold when excitatory synaptic activity predominates. This is known as *facilitation*. Successive stimulation of the same pre-synaptic fibre leads to *temporal summation*. This is providing the effect of preceding stimulus has not died away. Another form, *Spatial summation*, occurs when EPSPs originated at different places on the postsynaptic neuron summate.

#### 4.2.2. Excitatory neurotransmitters

Glutamic acid is the major *excitatory neurotransmitter* in the brain. Cortical neurones express different types of glutamate receptors (Monaghan et al., 1989; Watkins et al., 1990). These could fall into two major classes:

- (i) N-methyl-D-aspartate (NMDA) receptors are linked to calcium ( $\text{Ca}^{2+}$ ) channels, modulated by glycine (Thomson, 1990) and blocked by  $\text{Mg}^{2+}$  at resting potential. The block is relieved by depolarisation (Mayer et al., 1984).
- (ii) Non-NMDA receptors are divided into ionotropic receptors which are linked to sodium ( $\text{Na}^+$ ) and  $\text{Ca}^{2+}$  channels, and metabotropic receptors which are linked through G proteins to metabolic pathways. The phospholipase-C-linked metabotropic receptors are activated selectively by trans-1-amino-cyclopentane-1,3 dicarboxylate, referred to as ACPD (Siegelbaum and Kandel, 1991).

$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) are a class of non-NMDA ionotropic receptors (Blake et al., 1988) which are permeable to monovalent cations. AMPA receptors mediate non-NMDA fast excitatory postsynaptic potentials, whilst NMDA receptors mediate delayed  $\text{Ca}^{2+}$  and  $\text{Na}^+$  entry by initiating action potentials at an already depolarised membrane.

Ionotropic receptors directly gate ion channels and mediate fast, powerful responses allowing precise control of neuronal activity (Hille, 1992). In contrast, metabotropic glutamate receptors (mGluRs) indirectly modify the activity of ionic channels through second messenger-mediated cascades of intracellular enzymatic activities and mediate slow synaptic responses from seconds to minutes or even hours. Second messengers include  $\text{Ca}^{2+}$ , cyclic AMP, cyclic GMP, and phospholipid degradation products such as inositol triphosphate ( $\text{IP}_3$ ) and arachidonic acid. One of the most important roles of second messengers is to regulate phosphorylation reactions. Phosphorylation (adding or attaching a phosphate group to other proteins) alters the conformation of channel proteins in the membrane, thus altering membrane conductance, thereby increasing the activity of some cells and decreasing the activity of others. Kinases, calcium/calmodulin dependent kinase II (CamKII) and protein kinase C (PKC), are proteins that phosphorylate other proteins. Phosphorylation is commonly stimulated by transmitters and drugs that act via G protein-coupled receptors.

#### 4.2.3. Inhibitory synapses

Activation of an inhibitory synapse produces changes in the postsynaptic cell which lessen the likelihood that the cell will undergo an action potential. The combination

of the chemical transmitter with the receptor sites on the inhibitory subsynaptic membrane increases the permeabilities to potassium or chloride ions depending on the inhibitory receptor type, but not to sodium. The net effect is an increased negativity (*hyperpolarisation*) called an *inhibitory postsynaptic potential* (IPSP, figure 9). Increased potassium permeability at an activated inhibitory synapse makes the membrane potential closer to potassium equilibrium potential of -90 mV. This hyperpolarisation is of slow onset and is known as a slow or late IPSP lasting up to 100 msec. Thus, when a neuron is acted upon by an inhibitory synapse, its membrane potential is moved farther away from the threshold for activation of an impulse.

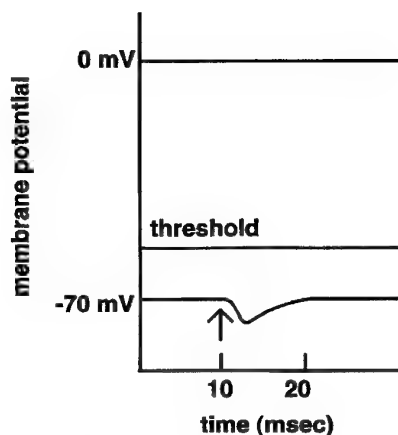


Figure 9. Inhibitory postsynaptic potential (IPSP). Stimulation of the presynaptic neuron is marked by the arrow.

The equilibrium potential of chloride is very close to the resting membrane potential. An increase in membrane permeability to chloride rapidly leads to inhibition. This greater chloride permeability is important when EPSPs and IPSPs arrive at the postsynaptic cell simultaneously because stabilisation of the membrane at its resting potential makes it less likely that it will change towards threshold for action potential generation.

#### 4.2.4. Inhibitory neurotransmitters

$\gamma$ -aminobutyric acid (GABA) is present within a large proportion of neurones in the CNS, where it is the major *inhibitory neurotransmitter* controlling synaptic transmission and neuronal excitability. Two distinct types of receptors mediate synaptic transmission by GABA in the CNS, GABA<sub>A</sub>- and GABA<sub>B</sub>-receptors (Bowery et al., 1981; Hill and Bowery, 1981).

GABA<sub>A</sub>-receptors are, by definition, linked to chloride channels, and are activated by isoguvacine, modulated by barbiturates and benzodiazepines, and antagonised by bicuculline. GABA<sub>A</sub>-receptors are comprised of a hetero-pentameric complex with at least 4 major subunit binding sites, together with an integral chloride ion channel (Kerr and Ong, 1992).

Activation of presynaptic GABA<sub>A</sub>-receptors normally leads to a net efflux of chloride ions causing partial depolarisation that blocks impulse transmission towards the

synaptic terminal, whereas activation of postsynaptic GABA<sub>A</sub>-receptors causes hyperpolarisation of the cell membrane and, thus, decreases sensitivity of the postsynaptic neurones to excitatory inputs (Krogsgaard-Larsen et al., 1988).

GABA<sub>B</sub>-receptors are heterogenous. They are located both pre- and post-synaptically, as well as on glial cells. The receptors are linked through different G proteins to pre-synaptic Ca<sup>2+</sup> and/or post-synaptic K<sup>+</sup> channels. Neuronal GABA<sub>B</sub>-receptors either inhibit Ca<sup>2+</sup> currents or activate K<sup>+</sup> currents depending on the cellular localisation of the receptor (Bowery, 1993).

Like GABA<sub>A</sub>-receptors, GABA<sub>B</sub>-receptors are found as presynaptic receptors, including autoreceptors, and as postsynaptic receptors. Presynaptic receptors modulate transmitter release from synaptic terminals, whereas autoreceptors inhibit the release of GABA itself, whilst postsynaptic receptors are responsible for inhibiting excitability of the postsynaptic cells. Thus depending on the brain region examined, GABA<sub>B</sub>-receptor activation can decrease neurotransmitter release, hyperpolarise postsynaptic neurones, or act presynaptically to inhibit GABA release at inhibitory neurones (Kerr and Ong, 1992).

Fast and slow types of excitatory and inhibitory synaptic responses are observed in central neurones. Fast IPSPs are produced by an increase in chloride permeability, and slow IPSPs by an increase in potassium permeability. It should however be noted that not all slow IPSPs in the brain are GABA generated (GABAergic), e.g. they can also be adrenergic and serotonergic.

#### 4.2.5. Presynaptic inhibition

As well as inhibition through activation of an inhibitory synapse which hyperpolarises the postsynaptic cell, a second type of inhibitory influence, called *presynaptic inhibition*, provides a means by which certain inputs to the postsynaptic cell can be selectively altered.

Presynaptic inhibition works by affecting the transmission at a single excitatory synapse. Transmitters are released in packets or quanta, each containing several thousand molecules. The presynaptic effect of the inhibitory transmitter would be to reduce the number of quanta released from the excitatory terminal. This synapse would, in turn, influence the postsynaptic cell, reducing the size of the EPSP.

Presynaptic inhibition naturally implies the existence of axo-axonic synapses between inhibitory and excitatory terminals. Also note that inhibitory neurones themselves can be inhibited presynaptically, whilst autoreceptors can be activated by diffusion of GABA from the synapse back onto the presynaptic region, thus inhibiting further transmitter release.

## 5. Synaptic Plasticity

Plasticity is the tendency of synapses and neuronal circuits to change as a result of activity. Synaptic plasticity is the basis for the informative connectionist neural models. It multiplies the complexity provided by any fixed cast of molecular characters or cellular functions.

Synaptic plasticity needs to capture all the information related to the features of pre- and postsynaptic activity, and has to produce long-lasting modifications in synaptic efficacy. There are many ways that synaptic efficacy might be altered. For example, transmitter release can be enhanced by a small increase in the amount of calcium that enters a nerve terminal with each action potential. The probability of postsynaptic receptor activation can be changed, and on a longer time scale, variations in activity can alter the number of functional receptors. In order to produce a permanent memory store, *de novo* synthesis of ion channels, neurotransmitter receptors, or other proteins in synaptic structures, are envisioned as possibilities. Beyond changes in the function of synapse, activity may alter the number or location of synapses themselves. Axons sprout new endings when their neighbours become silent, and the terminal branches of dendritic arbors are constantly remodelled. Therefore elongation and branching of dendrites and additional budding of spines at synaptic junctions may be amongst changes occurring in synaptic structures to explain persistence of a memory.

Proteins are degraded on a time scale that ranges from minutes to days. Maintenance of memories that may last a lifetime requires more stable alterations, such as those associated with persistent changes in gene expression. A recently discovered family of genes called *immediate early genes* (IEGs), which are not normally active, but are activated rapidly by brief bursts of action potentials, may provide a crucial link. As expected of master switches that initiate long term changes in the brain, IEGs encode transcription factors (Cole et al., 1989; Wisden et al., 1990), proteins that regulate the expression of other genes. Some evidence has been obtained that impulse activity increases the expression of genes that encode trophic factors, proteins that promote the survival of neurones. Additionally, genetic approaches have established that the transcription factor CREB is involved in long-term memory (Schulman, 1995; Bartsch et al., 1995). Postsynaptic CREB phosphorylation via calmodulin and a  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase is shown to be evoked by synaptic stimuli, including those inducing potentiation and depression of synaptic strength (Deisseroth et al., 1996). Thus, the adage "use it or lose it" may well have a specific biochemical correlate. In addition to protein kinases, there is evidence for the involvement of proteases (calpain) and phospholipases (phospholipase  $\text{A}_2$ ) in the biochemical processes associated with several forms of synaptic plasticity (Massicotte and Baudry, 1990). These play a critical role in the initiation of long-term synaptic potentiation and long-term depression, as well as in the induction of genes that permit long-term expression of altered synaptic states (Schulman, 1995).

## 6. Associative Learning

Donald O Hebb in his book, *The Organisation of Behavior*, in 1949 suggested a relationship as a basis for the formation of new neural ensembles during learning. He proposed that association could be formed by coincident neural activity: "When axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that efficacy of A, as one of the cells firing B, is increased." Thus a "Hebbian" synapse becomes stronger if the neurones it links to are both active at the same time (see figure 10).

Ladislav Tauc and Eric Kandel proposed a second associative learning rule in 1963 while working at the institute Marey in Paris on the nervous system of the marine snail *Aplysia*. They found that the synaptic connection between two neurones could be strengthened without activity of the postsynaptic cell when a third neuron acts on the presynaptic neuron. The third neuron, called a modulatory neuron, enhances transmitter release from the terminals of the presynaptic neuron. They suggested this mechanism could take on associative properties if action potentials in the presynaptic cell were coincident with action potentials in the modulatory neuron (a pre-modulatory associative mechanism). This association is shown in figure 10.

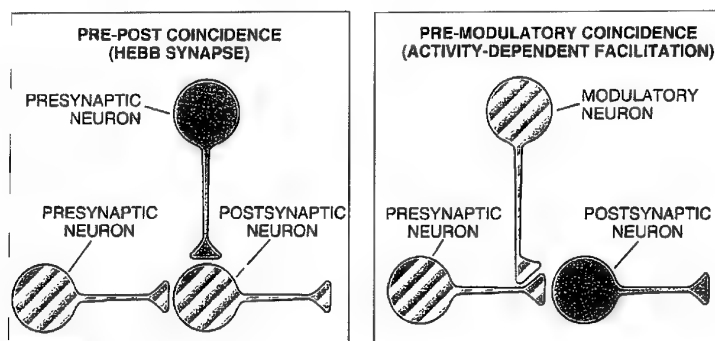


Figure 10. Two cellular mechanisms that are hypothesised for associative changes in synaptic strength during learning.

In general, however, some synaptic modifications have been found that are not Hebbian. Figure 11 shows variations in conditions for induction and site of expression of plasticity, each of which requires concurrent activity in two elements.

### 6.1. Classical conditioning mechanism in *Aplysia* - An implicit form of learning

*Aplysia* is used in studies of the biological basis of learning because its simple nervous system consists of only 20000 relatively large neurones. The gill-withdrawal reflex has been well studied, where the animal withdraws the gill in response to a stimulus being applied to another part of its body such as the mantle shelf or the fleshy extension called the siphon. An increase in the release of neurotransmitter due to activity-dependent facilitation is a mechanism that contributes to conditioning. The molecular steps in activity-dependent facilitation are shown in figure 12. Serotonin released from the modulatory neuron by an unconditioned stimulus

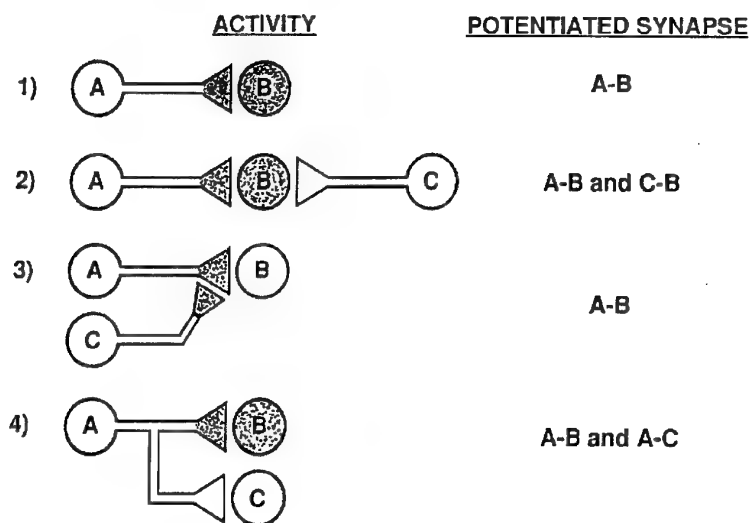


Figure 11. Various forms of potentiated synapses. (1) Traditional Hebbian synapse. (2) The same conditions for induction lead also to potentiation of another synapse (C-B) from an unstimulated Cell, C. This is heterosynaptic potentiation. In (3) the condition for induction involves the activity in neurones A and C, and even though activity in B is not required, the A-B synapse may be potentiated nonetheless. This is known as pre-modulatory coincidence mechanism. In (4) concurrent activity in A and B is needed to trigger plasticity at the A-B synapse, but once triggered, then synapses between A and other neurones, e.g. A-C, are strengthened (from Churchland and Sejnowski, 1992).

activates an enzyme called adenylyl cyclase in the sensory neuron. When the sensory neuron is active, levels of calcium are elevated within the cell. The calcium binds to calmodulin, which in turn binds to adenylyl cyclase, enhancing its ability to synthesise cyclic AMP from ATP. The cyclic AMP then acts as a second messenger and activates a protein kinase, which leads to the release of a substantially greater amount of transmitter than occurs normally. This increase in transmitter is due to an increase in calcium influx, and also due to action of serotonin in mobilising transmitter vesicles from a storage pool to the release sites at the membrane. In the latter action, cyclic AMP acts in parallel with protein kinase C. Cyclic AMP plays an important role in certain elementary types of implicit learning and memory storage, as it also activates a number of potassium channels. Phosphorylation of potassium channels, which regulate the duration of depolarisation exhibited by presynaptic terminals invaded by an action potential, also regulates the amount of transmitter release at synapses (Kandel, 1982).

This model which readily accounts for short-term regulation of transmitter release, has been further elaborated to incorporate links between second messengers and the transcription apparatus of the cell (Mayford et al., 1992) so as to account for the long-term modifications in transmitter release to subserve long-term changes in synaptic efficacy. Sudhof et al. (1989) later proposed a model in which phosphorylation of a protein associated with synaptic vesicles regulates the pool of vesicles that can participate in transmitter release. Cyclic AMP second-messenger system plays an



important role in the persistent phase of such long-term modifications (Schulman, 1995).

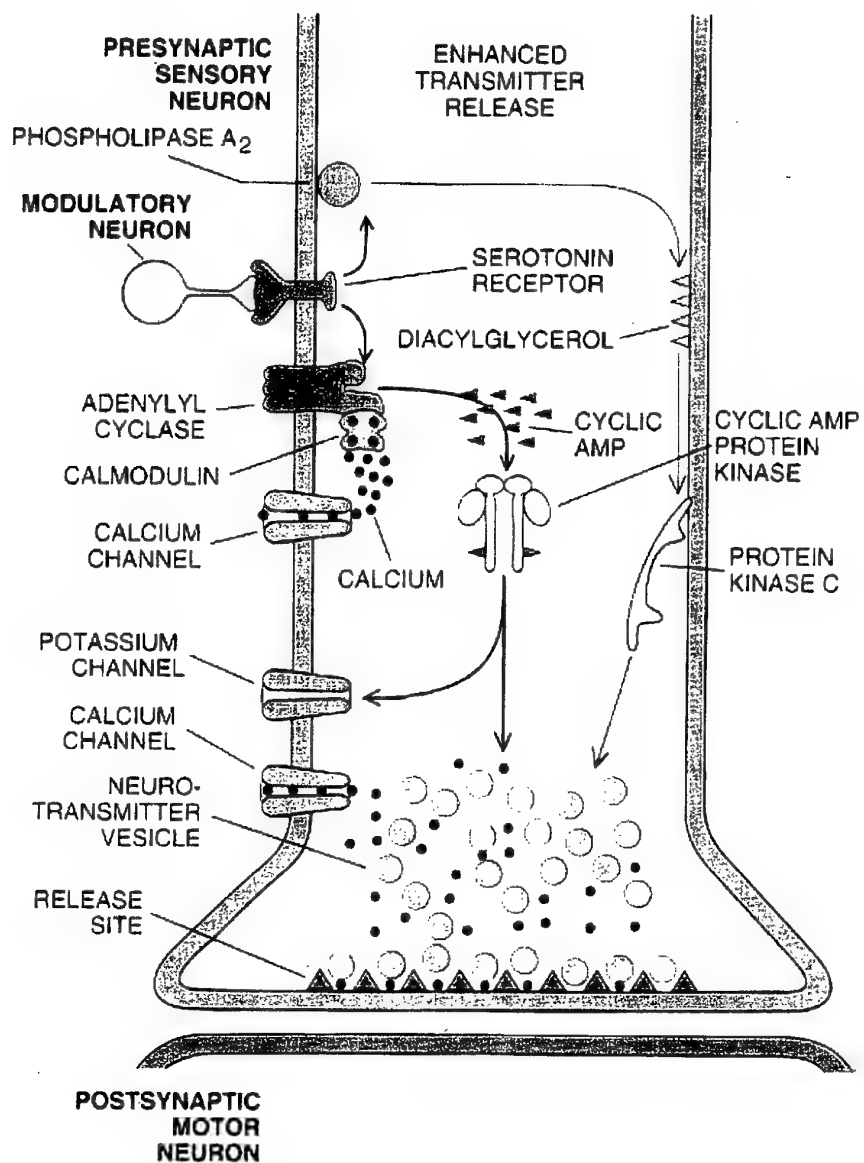


Figure 12. Biochemical processes associated with classical conditioning in *Aplysia*, an implicit form of learning.

## 7. Long-Term Synaptic Potentiation

It is difficult to find cellular changes that are identifiable as learning dependent. This is because minimally it must be shown that the changes are directly owed to effects of experience, and it must be shown that the changes in behaviour are dependent on cellular modifications. As well, it must be shown that there is modification in the cell's responses to the test stimulus, and that the modification lasts beyond the duration of the learning phase. Evidently, single-cell recordings, extracellular or preferably intracellular, are needed to determine whether these circumstances obtain. This can be exceptionally tricky for a number of reasons. For example, the prime postsynaptic site will obviously be on dendrites, and these tiny structures present great obstacles to intracellular recording. Controlling the cell's input, voltage, and diachronic biography is generally a very pernicky art. Care must be taken to exclude changes that might be occurring in other parts of the circuit, such as a network of inhibitory interneurons.

*Long-term potentiation* (LTP) is a persistent increase in synaptic efficacy that follows brief periods of stimulation. Attention has focused on synapses in the hippocampus because clinical and experimental data have identified it as a critical structure for the process of memory consolidation (Milner, 1972) and spatial memory (O'Keefe and Nadel, 1978). This region of the cortex is implicated in forms of memory that require conscious deliberation.

### 7.1. Functional anatomy of the hippocampus

As shown in figure 13, afferents from entorhinal cortex that make excitatory synapses on granule cell dendrites form the perforant path. Mossy fibres are granule cell axonal tracts in dentate gyrus that form excitatory synapses onto CA3 pyramidal cells. The dentate gyrus is separated from the hippocampus by hippocampal fissure. CA3 pyramidal cell axonal tracts that form excitatory synapses onto CA1 pyramidal cells are known as Schaffer collaterals.

### 7.2. Long-term potentiation in the hippocampus

In 1973, Terje Lømo, Tim Bliss and Tony Gardner-Medwin, while using microelectrodes to study electrical activity in the brain of rabbits in Per Andersen's laboratory in Oslo, Norway, found that sending sustained volley of artificial impulses (tetanic stimulation; 100 Hz, for 1 second) along the perforant path fibres entering the dentate gyrus of hippocampus resulted in a dramatic and long-lasting increase in the strengths of the synapses of granule cells. They tested the responses of postsynaptic cells to a low-frequency pulse before and after the experimental manipulation and discovered that the postsynaptic excitability was potentiated after the volley and remained potentiated for hours, as long as they could keep the preparation intact. They called this discovery Long-Term Potentiation (Bliss and Gardner-Medwin, 1973; Bliss and Lømo, 1973).

Long-term potentiation is typically induced with high frequency stimulus trains (50-400 Hz, 1-2 s). Such a high-frequency stimulation largely exceeds the normal physiological firing range. The induction of LTP by temporal pattern stimulation has been demonstrated using stimulus patterns that mimic the neural activity of the natural theta rhythm. Theta stimulation is composed of brief high-frequency bursts

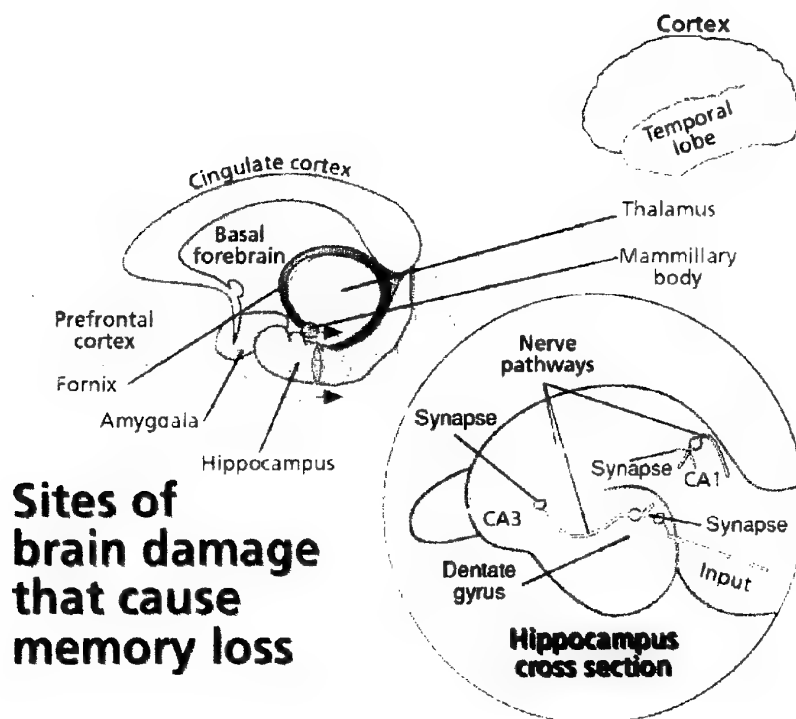


Figure 13. Memory hardware including hippocampus and cortex. Some major excitatory synaptic pathways of hippocampus are also shown. The hippocampus is thought to be involved in storing recently learned information, while the cortex is essential for "working" memory and storing older memories.

(4-10 pulses at 200 Hz) delivered at 170-200 msec intervals. The enhancement of the NMDA component of the EPSP, when stimuli are delivered 200 ms apart, suggest that activity-dependent disinhibition would enable repetitive stimulation at a frequency of 5 Hz to induce long-term potentiation. Indeed, several studies report that stimuli or group of stimuli, delivered 200 ms apart, are extremely effective at inducing LTP. For example, Larson and Lynch (1986) report that LTP could be induced in area CA1 by as little as four stimuli delivered at 100 Hz, when these stimuli were delivered 200 ms after a similar group of pulses, called the "priming" stimulus. Alternatively, LTP can be induced by a burst of 2 to 10 stimuli at 100 Hz delivered about 200 ms after a single priming stimulus (Rose and Dunwiddie, 1986; Diamond et al., 1988). This type of priming stimulation has been reported to be effective in inducing LTP in the dentate gyrus and area CA1 both *in vivo* and *in vitro* (Larson et al., 1986; Larson and Lynch, 1989; Rose and Dunwiddie, 1986; Diamond et al., 1988). Tsukada et al. (1994) found that the magnitude of the induced LTP in CA1 differed largely according to the difference in the time structure in the interstimulus intervals of stimuli which had the same pulse number and the same mean frequency. Therefore, the temporal factors given by different correlations between successive inter-spike intervals are important in modulating the synaptic weight of CA1 neurones.

LTP is rapidly induced. Immediately following high-frequency stimulation of pre-synaptic axons, the size of the EPSP transiently increases to up to 500% of its baseline

value. Most of this increase decays to a level 30 to 200% above baseline within about 5 minutes after tetanic stimulation. The early potentiation, lasting about 1 minute, is called post-tetanic potentiation (PTP), and may be due to short-term accumulation of calcium ions in the presynaptic terminal (Delaney et al., 1989). The persistent phase is known as LTP. Once induced, LTP is expressed as a persistent and synapse-specific increase in the amplitude of synaptic responses elicited by low-frequency stimulation of the excitatory afferents (see figure 14). All three major excitatory pathways of the hippocampus support LTP. These consist of axonal projections from the entorhinal cortex to the dentate gyrus (perforant path), dentate gyrus to area CA3 (mossy fibres), and area CA3 to area CA1 (Schaffer collaterals).

For more than a decade after its discovery, LTP's Hebbian behaviour baffled neuroscientists. It seemed that certain synapses had a mechanism for detecting when both the pre- and post-synaptic neurones, were simultaneously active. The breakthrough in finding the mechanism involved came in early 1980s with the discovery of a receptor known as the NMDA receptor.

The forms of LTP that occur in the perforant path-dentate granule cell synapse and the Schaffer collateral-CA1 pyramidal cell synapse are NMDA dependent (Collingridge et al., 1983; Morris et al., 1986; Errington et al., 1987), and have Hebbian characteristics (Brown et al., 1990). This Hebbian feature endows LTP in CA1 with *associativity*. When weak stimulation of one afferent pathway (which is itself insufficient to produce LTP) is temporally paired (or associated) with strong stimulation of another input pathway (capable of producing LTP), the weak pathway also undergoes LTP. This is shown in figure 15. By contrast, LTP in the mossy fibre to CA3 region does not depend on NMDA receptor activation, is not Hebbian, and is not associative (Chattarji et al., 1989; Staubli et al., 1990; Zalutsky and Nicoll, 1990). In fact under some conditions, LTP induction at Schaffer collateral synapses in hippocampal area CA1 is reported not to require NMDA receptor activation (Grover and Teyler, 1990).

Llinas and colleagues (Alonso et al., 1990) studied cells in layer II in slices of entorhinal cortex of the guinea pig and found non-Hebbian as well as Hebbian types of LTP. The Hebbian effect was found in the classical way, namely high-frequency tetanus delivered to the presynaptic fibres. The non-Hebbian effect was achieved by injecting a 5-Hz oscillating current into the postsynaptic cell itself for about 20 sec. Also, unlike Hebbian type, all the synapses of the cell receiving the oscillating current were affected. Llinas found through experiments with a NMDA receptor antagonist, AP5, (also known as APV; 2-amino-5-phosphonopentanoic acid), that NMDA receptor is critical for maintenance as well as induction of this non-Hebbian type of LTP.

The presynaptic terminals of hippocampal synapses release an excitatory amino acid transmitter, which is most likely glutamate (Cotman and Nadler, 1981). This stimulates receptor molecules embedded in the membrane of postsynaptic neurones on specialisations known as dendritic spines. These small protuberances are connected to the dendrite by a thin neck (Harris and Landis, 1986). The receptors respond by opening channels in the membrane of the neuron, admitting ions and so triggering an electrical impulse. In the hippocampus the ionotropic receptors are of two main types, called AMPA and NMDA after chemicals that trigger them with particular vigour. AMPA receptors are permeable to monovalent cations (Jahr and

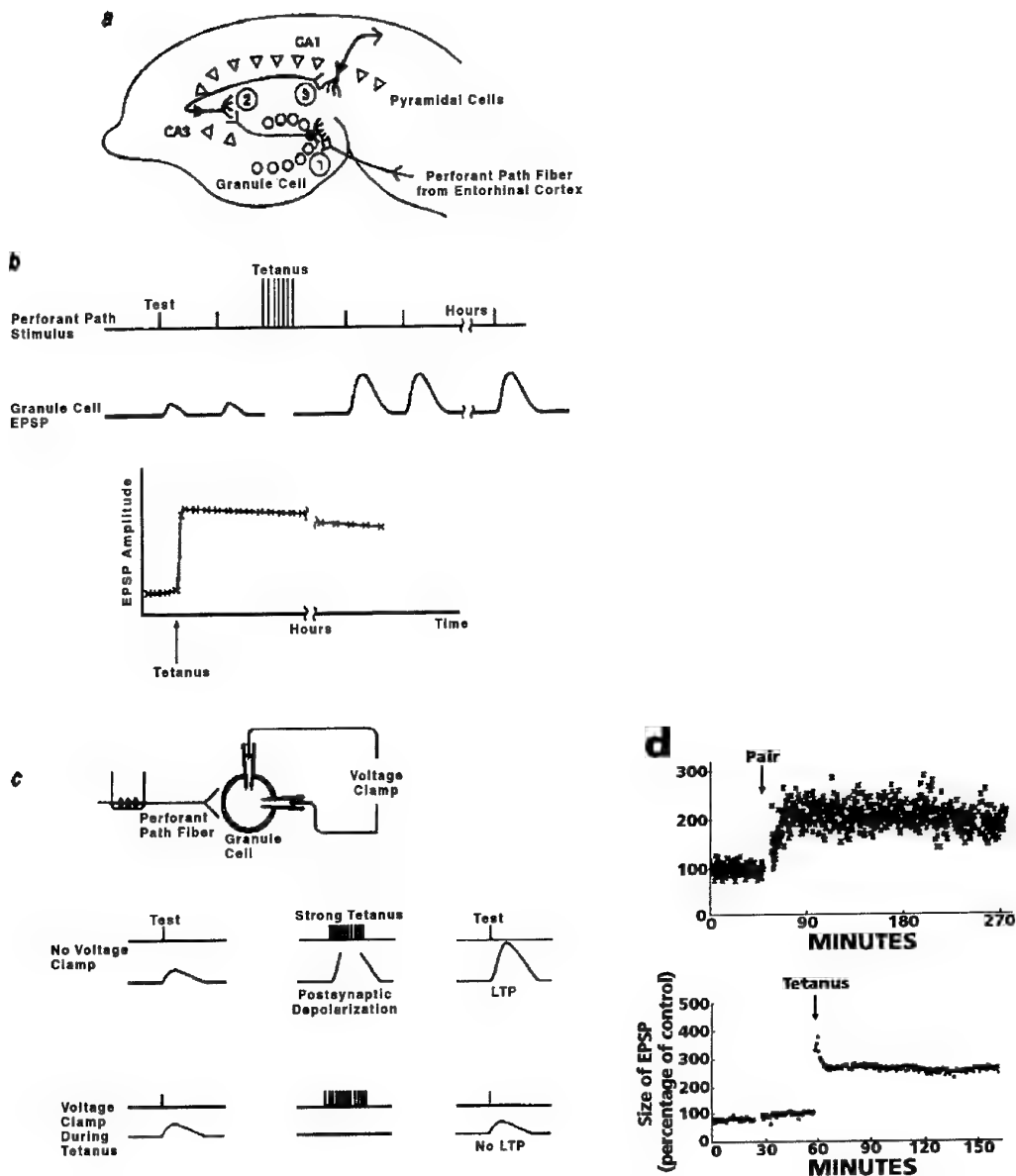


Figure 14. Long-term synaptic potentiation (LTP) in the hippocampus. (a) Schematic drawing of a hippocampal slice. (b) LTP of the perforant path to granule cell neuron synapse. (c) When the postsynaptic cell is voltage-clamped to prevent depolarisation during the tetanus, even a strong tetanic stimulus does not produce LTP. This implies that LTP is essentially Hebbian. (d) LTP can be induced by two methods. Lower graph: tetanic stimulation of presynaptic axons causes a short-lasting potentiation (post-tetanic potentiation, or PTP) followed by a persistent potentiation of the EPSP (LTP). Upper graph: low-frequency stimulation of presynaptic axons paired with artificial depolarisation of the postsynaptic cell through current injection by an intracellular electrode also produces LTP, but no PTP (a, b and c from Levitan and Kaczmarek, 1991. *The neuron: Cell and Molecular Biology*. Oxford University Press; d from Madison and Schuman, 1991).

Stevens, 1987; Mayer and Westbrook, 1987; Ascher and Nowak, 1988a), and are responsible for routine transmission across synapses. NMDA receptors are permeable to  $\text{Na}^+$  and  $\text{Ca}^{2+}$  (MacDermott et al., 1986), but current flow through this channel is normally prevented by extracellular  $\text{Mg}^{2+}$  binding to a site within the open channel, blocking the flow of other ions (Mayer and Westbrook, 1987). NMDA receptors put Hebb's rule into effect. This is because unlike most receptors, the NMDA receptor requires two triggers before it will activate to allow ionic traffic. The presynaptic neuron must deliver glutamate to bind to the receptor and the

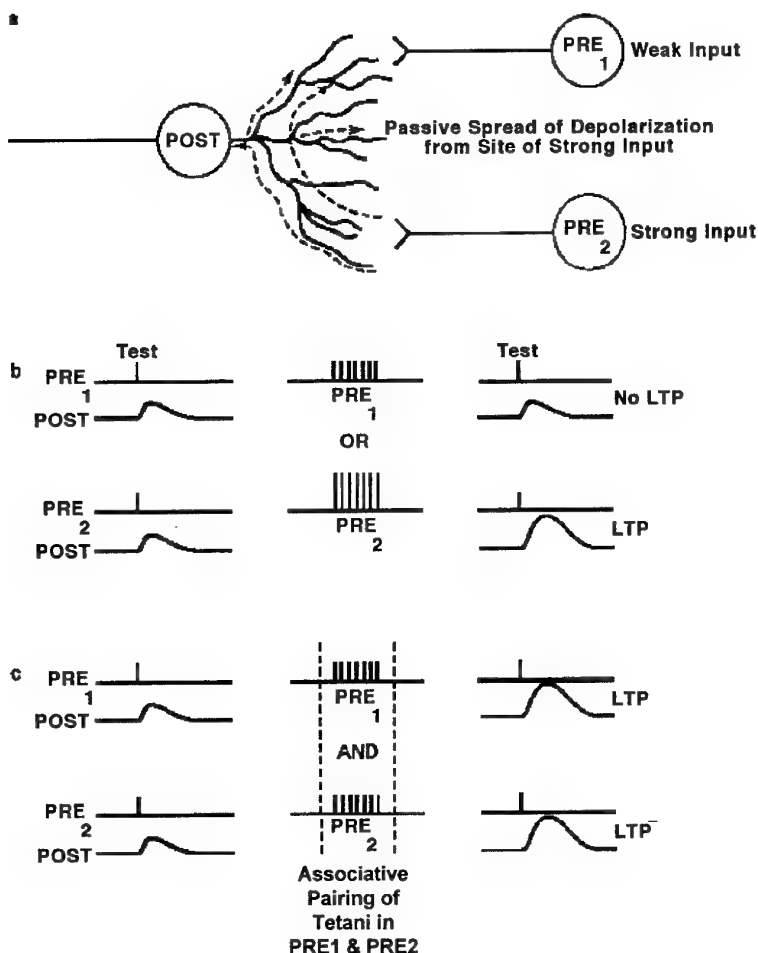


Figure 15. Associative long-term potentiation. (a) Diagram depicting spatial relationships between a strong and a weak synaptic input. (b) Stimulation of the strong input produces LTP, but stimulation of the weak input alone does not. (c) When the strong and weak inputs are paired, the depolarisation produced by the strong input spreads to the site of the weak input and contributes to the induction of LTP.

postsynaptic neuron must coincidentally depolarise to dislodge magnesium ions blocking the NMDA channel (Mayer et al., 1984). This phenomenon may well occur by an electrostatic interaction between the divalent cation and the membrane potential (Madison and Schuman, 1991).

The level of postsynaptic depolarisation required for LTP induction is only satisfied when a sufficient number of afferent fibres and synapses are activated. This property is called *cooperativity* (McNaughton et al., 1978). Thus, the NMDA receptor has associative or coincidence-detecting properties much as does the adenylyl cyclase in the implicit form of learning. However the temporal characteristics of NMDA receptors, a requirement for simultaneous activation, are better suited for explicit rather than implicit forms of learning. Additionally, as Hebb's rule demands, both events require neurones to be activated.

During low-frequency transmission, significant activation of the NMDA receptor system in the CA1 region of the hippocampus is prevented by GABA mediated synaptic inhibition which hyperpolarises neurones into a region where NMDA receptor-operated channels are substantially blocked by  $Mg^{2+}$ . However during high frequency transmission, mechanisms are evoked that provide sufficient depolarisation of the postsynaptic membrane to reduce this block and thereby permit the induction of LTP. Davies et al. (1991) propose that this critical depolarisation is enabled because, during high-frequency transmission, GABA depresses its own release by an action on  $GABA_B$  autoreceptors. This permits sufficient NMDA receptor activation for the induction of LTP. Therefore during high-frequency stimulation a critical factor for the induction of LTP is depression of synaptic inhibition, brought about by the activation of  $GABA_B$  autoreceptors.

During tetanic stimulation, EPSPs resulting from activation of the AMPA receptors overlap and summate, producing a depolarisation large enough to relieve the  $Mg^{2+}$  block of the NMDA channels. It is this need for depolarisation that makes tetanic stimulation effective in inducing LTP, while low frequency stimulation is ineffective. This idea is reinforced by demonstrations that artificial depolarisation of the postsynaptic cell, via current passed through a microelectrode, coupled with low-frequency stimulation can induce LTP (Stanton and Sejnowski, 1989). The artificial depolarisation (20 mV) prevents the blockade of the NMDA channel by  $Mg^{2+}$  so that when the transmitter is released it is able to produce current flow through the NMDA channel. This is shown in figure 16.

Once NMDA receptors open, they stay open for 100-200 msec during which there is an influx of  $Ca^{2+}$  (MacDermott et al., 1986) which, together with the activity of mGluRs, spark off a cascade of biochemical changes that bring about LTP.

The NMDA receptor thus perhaps lies at the molecular heart of memory. Manipulations that prevent NMDA receptor activation such as postsynaptic hyperpolarisation (Malinow and Miller, 1986), application of NMDA receptor antagonists (Collingridge et al., 1983; Maren et al., 1991 and 1992;), blocking the ionophore (Abraham and Mason, 1988), or intracellular injections of  $Ca^{2+}$  chelators (Lynch et al., 1983; Malenka et al., 1988) prevent LTP induction. In addition, potentiation is induced when the level of postsynaptic  $Ca^{2+}$  is artificially raised (Malenka et al., 1988).

Calcium influx into the postsynaptic cell through the unblocked NMDA receptor channel is critical for long-term potentiation, as it activates different types of protein kinases, including PKC and CamKII. Inhibitors of PKC and CamKII enzymes prevent the induction of LTP (Muller et al., 1990; Muller et al., 1994), and produce learning impairment in a number of behavioural paradigms including peck

avoidance in chicks (Burchuladze et al., 1990; Serrano et al., 1994; Serrano et al., 1995) and avoidance learning in rats (Jerusalinsky et al., 1994). It has been reported that both short term memory and maintenance of LTP are particularly affected by the inhibitors of CamKII and PKC ((Izquierdo and Medina, 1995). Moreover, discrimination learning in rats is associated with a redistribution of hippocampal PKC (Olds et al., 1990). In recent years, mice deficient in genes coding for such enzymes involved in LTP induction have been found to exhibit learning impairments (Grant et al., 1992; Silva et al., 1992; Abelovich et al., 1993a; Abelovich et al., 1993b).

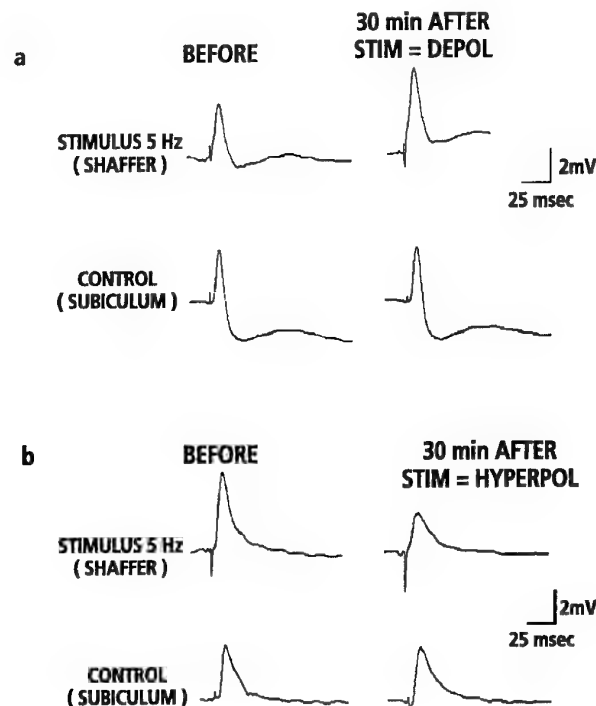


Figure 16. Pairing postsynaptic depolarisation with synaptic stimulation of synapses on CA1 hippocampal pyramidal neurones produces synapse-specific LTP, while pairing of postsynaptic hyperpolarisation with stimulation of synapses produces synapse-specific long-term depression (LTD). (a) Intracellular evoked EPSPs are shown at stimulated (stimulus 5 Hz, Schaffer) and unstimulated (control, subiculum) pathway synapses before and 30 minutes after pairing depolarising current injection with 5-Hz synaptic stimulation. The stimulated pathway exhibits associative LTP of the EPSP whereas the control, unstimulated input shows no change in synaptic strength. (b) Intracellular EPSPs evoked at stimulated and control pathway synapses before and 30 minutes after pairing a 20 mV hyperpolarisation at the cell soma with 5-Hz synaptic stimulation. The 5 Hz stimulus input activated during the hyperpolarisation shows associative LTD of synaptic evoked EPSPs, while synaptic strength of the silent input (control) is unaltered (from Stanton and Sejnowski, 1989).



Research indicates that mGluRs are also required for LTP induction in the hippocampus (Riedel and Reymann, 1993; Bortolotto et al., 1994), for both NMDA receptor-dependent and NMDA receptor independent forms (Bashir et al., 1993). Memory and LTP are blocked early on by antagonists of mGluRs (Izquierdo and Medina, 1995).

One of the most longstanding questions regarding LTP is whether it occurs as a result of persistent changes in the presynaptic terminal or in the postsynaptic cell. The very small size of brain synapses has hindered the direct experimental measurements that would resolve this question. It is useful to break the hypothetical LTP mechanisms down into three conceptual processes: *Induction*, *maintenance*, and *expression*. Induction refers to those processes that are involved in the initiation of LTP. Maintenance describes events that transfer induced potentiation into a sustained temporal domain. The maintenance processes are the changes that make LTP persist. The expression of LTP refers to processes responsible for “reading out” the maintained plasticity. Disruption of expression mechanisms may result in a reversible attenuation of LTP, since the plasticity is still sustained by the cellular mechanisms responsible for maintenance.

### 7.2.1. Induction of LTP

It is clear that there is a discrete and separable induction phase of LTP because NMDA antagonists and several protein kinase inhibitors block LTP if applied during, but not after, tetanic stimulation.

This component of LTP is postsynaptic since manipulations that affect only the postsynaptic cell can influence the induction of LTP. The injection of  $\text{Ca}^{2+}$  chelators and of protein kinase inhibitors into the postsynaptic cell, or preventing a postsynaptic cell from depolarising either by passing hyperpolarising current or by voltage clamping the postsynaptic membrane (see figure 14, c), can prevent LTP (Malinow and Miller, 1986; Kelso et al., 1986).

The induction of LTP therefore appears to depend on postsynaptic depolarisation, leading to the influx of calcium and the subsequent activation of second messenger kinases which phosphorylate proteins. Phosphorylation reactions that modify ionic channels, neurotransmitter receptors, or synaptic proteins involved in the regulation of transmitter release are potential candidates for producing at least short-term regulation of synaptic efficacy (Hemmings et al., 1989).

### 7.2.2. Maintenance of LTP

The nature and location of the modifications responsible for the long-term maintenance and expression of synaptic efficacy, on the other hand, are still a matter of controversy (Baudry and Davis, 1991). Initially, Bliss et al. (1986) provided evidence for enhanced presynaptic release of glutamate during LTP. Since then most of the information available regarding both the cellular mechanisms and the synaptic locus of LTP maintenance has been gained through experiments with protein kinase inhibitors (Malinow et al., 1988). Experimental advantage can be taken by comparing the effects of inhibitors injected into a postsynaptic cell versus bath-applied, where the inhibitor can interact with both pre- and postsynaptic elements. Davies et al. (1989) applied glutamate agonists iontophoretically to the postsynaptic cell and

found no change in receptor responsiveness soon after the induction of LTP, but an increase during later stages of LTP, suggesting that maintenance is initially presynaptic and only later becomes postsynaptic. A number of other studies provide evidence for a presynaptic site of maintenance. For example, results from an experiment with a protein Kinase inhibitor, H-7, by Malinow et al. (1989) suggest that a constitutively active kinase that maintains LTP resides in a location other than the postsynaptic cell, possibly in the presynaptic terminal. Similarly, Hess and Gustafsson (1990) indicate that LTP is associated with a change in shape of the excitatory synaptic potential, perhaps consistent with spike broadening in the presynaptic terminals. Bashir et al. (1991) report an increase in the NMDA component as well as the non-NMDA component of the synaptic potential during tetanic stimulation, indicating that there is an increase in presynaptic neurotransmitter release during LTP. This is contrary to earlier studies by Kauer et al. (1988) and Muller et al. (1988) which found that during LTP only the flow of current through the non-NMDA-receptor channels was enhanced.

### 7.2.3. Expression of LTP

The most popular and conservative view is that LTP expression involves both pre- and post-synaptic changes (Malgaroli, 1994). There are three broad possibilities for the types of mechanisms that could cause the synapse to transmit more strongly. These are shown in figure 17. One possibility is that the sensitivity of the postsynaptic cell to neurotransmitter is increased. This could occur for several reasons, for example, as a result of an increased number of neurotransmitter receptors, an increased affinity of neurotransmitter receptors, or an increased current flow through the glutamate ionophores. The responsiveness of ionotropic receptors reflects several parameters including the mean open time and conductance of the channel as well as the affinity of the receptor for neurotransmitter (Ambros-Ingerson and Lynch, 1993). It has been demonstrated that, following the establishment of LTP, the responsiveness of postsynaptic cells to exogenously applied AMPA increases (Davis et al., 1989), and the fast component of EPSP is preferentially enhanced (Kauer et al., 1988; Muller and Lynch, 1988). Another possibility is that a morphological change would occur in the hippocampal synapses (Applegate et al., 1987) that would increase synaptic efficacy. An example of such a change would be an increase in the width of the postsynaptic spine neck which, due to reduced resistance, would allow greater current flow from the postsynaptic spine and the main shaft of the dendrite, resulting in a greater synaptic potential. Thus such structural modifications of the dendritic spine can, in effect, influence postsynaptic responsiveness to transmitter (Wilson, 1988). A third possibility is that LTP expression could result from an increase in presynaptic neurotransmitter release by a variety of mechanisms. It has been shown that the concentration of glutamate in the extracellular fluid in the hippocampus increases after tetanic stimulation and remains elevated for as long as LTP persists (Bliss et al., 1986), but it has not been ascertained whether the increase is due to tetanisation of synaptic terminals. Furthermore, such an increase in glutamate could occur as a result of a decrease in glutamate uptake, rather than an increase in release.

Detailed mechanism underlying neurotransmitter release are not yet understood. An ongoing debate has divided researchers who support the hypothesis that exocytosis of synaptic vesicles accounts for the quantal nature of transmitter release (De Camilli and Jahn, 1990) and those who argue against such a hypothesis and suggest the

existence of specialised molecules, mediators, that play a critical role in the release process (Israel & Morel, 1990).

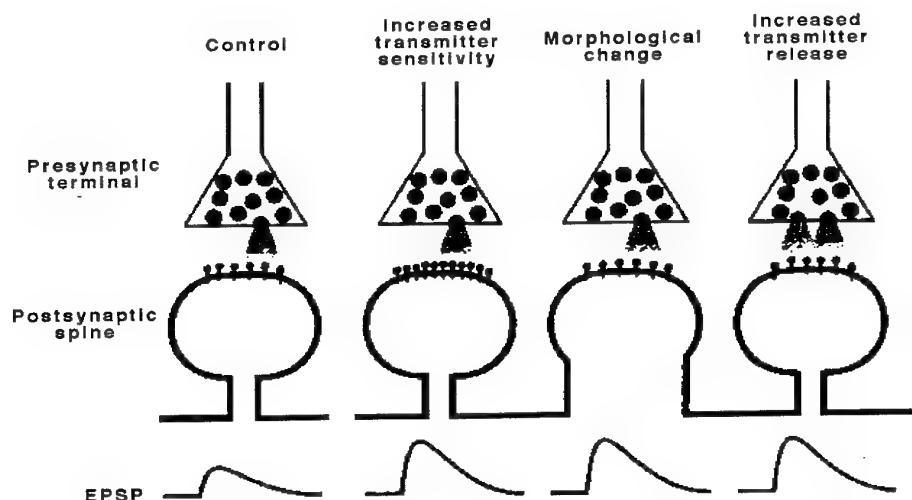


Figure 17. Schematic diagram representing three general mechanisms for LTP expression through a series of aggregate synapses. Presynaptic terminals containing synaptic vesicles, postsynaptic spines containing transmitter receptors; and below, control and potentiated EPSPs are shown (from Madison and Schuman, 1991).

Quantal analysis is, however, the most direct method of differentiating pre- from postsynaptic mechanisms involved in changes in synaptic strength (Siegelbaum and Kandel, 1991). This method takes advantage of the probabilistic nature of the presynaptic release of transmitter from vesicles. Variations of quantal analyses on whole-cell recordings have been conducted which show an increase in the probability of presynaptic transmitter release (Bekkers and Stevens, 1990; Malinow and Tsien, 1990). Attempts have been made during these studies to reduce the number of activated synapses by reducing the strength of applied stimulation, or even more satisfying, to impale a single neurone that projects to the postsynaptic cell either in culture (Bekkers and Stevens, 1990) or in a slice preparation (Malinow, 1991). Although it has been shown by several studies that there is little variability in evoked quantal size (Edwards et al., 1990; Malgaroli and Tsien, 1991; Malinow, 1991), and that the enhancement in synaptic responses is best explained by presynaptic increase in quantal transmitter release (Kullmann and Nicoll, 1992; Larkman et al., 1992; Liao et al., 1992), another quantal study of LTP shows an increase in quantal size, but not quantal content, of the EPSP (Foster and McNaughton, 1991). These investigations do not as yet provide definitive evidence in favour of a presynaptic mechanism for LTP expression. Some caveats regarding quantal analyses of hippocampal excitatory transmission has been raised, namely the transmitter release often deviates from a simple binomial or Poisson distribution (Larkman et al., 1991), or that an increase in the number of postsynaptic receptor clusters should not be interpreted as an increase in the number of vesicles released (Edwards, 1991). These suggest that a cautious approach should be taken in the interpretation of quantal analysis when attempting to assign a pre- or postsynaptic locus of LTP expression (Faber and Korn, 1991; Schweizer et al., 1992; Stevens, 1993).

An alternative approach that has been used is the analysis of spontaneous synaptic events or minis (mini EPSPs or mini IPSPs, Malgaroli and Tsien, 1992; Manabe et al., 1992). Minis are thought to be synaptic responses to single packets of transmitter and they are generally seen as isolated events, facilitating distinctions between quantal size and release probability. The study of spontaneous miniature events have been used to reveal postsynaptic changes following LTP. Manabe et al. (1992) by measuring the amplitude of minis detected increases in quantal size, consistent with a postsynaptic enhancement. Malgaroli and colleagues observed that the frequency of mini excitatory postsynaptic currents was increased strongly after glutamate-induced synaptic enhancement, and that the mini frequency potentiation was not related to an increase in presynaptic  $\text{Ca}^{2+}$  influx. Thus, Malgaroli (1994) suggests that the expression of LTP involves an increase in the efficiency of some internal steps in the secretory process.

For the maintenance and expression of LTP, more complex reactions linking enzymatic cascades to structural modifications of synaptic contacts are probably necessary to produce long-lasting modifications of synaptic transmission. Several groups of researchers have found that enhancement of transmitter (glutamate) from the presynaptic terminal is involved (Bliss et al., 1990; Malinow, 1991; Schuman and Madison, 1991; Malgaroli and Tsien, 1992), while others refer to a postsynaptic changes in glutamate AMPA receptors (Davies et al., 1989; Manabe et al., 1992; Staubli et al., 1992; Maren et al., 1993). Another possibility is that LTP expression is mediated by a structural modification of the synapse, possibly involving transmembrane proteins such as integrins (Wallace et al., 1991; Xiao et al., 1991).

Substantial isolation of spine compartments from the main dendritic compartment in neurones with large dendritic trees and numerous spine synapses represents a serious problem for the integration of spatially distal events. Several mechanisms are likely to contribute to the spatial propagation of electrical and chemical signals through out the postsynaptic neuron. For instance, both the rapid diffusion of second messengers into the dendritic compartment, as well as active propagation of membrane potential changes along the dendritic membrane, constitute signalling mechanisms that incorporate spatial information.

If the maintenance and expression processes are presynaptic, then as first proposed by Bliss, some message must be sent from the postsynaptic neuron to the presynaptic neuron across the synapse (Kennedy, 1988). This poses a problem for neuroscientists. Ever since the great Spanish anatomist Santiago Ramon Y Cajal first enunciated the principle of dynamic polarisation about 100 years ago, every chemical synapses studied has proven to be unidirectional. Information flows only from the presynaptic to the postsynaptic cell. In LTP, a new principle of nerve cell communication seems to be emerging. The calcium-activated second-messenger pathways, or perhaps calcium acting directly, seem to cause release of a retrograde plasticity factor from the active postsynaptic cell. This retrograde factor then diffuses back to the presynaptic terminals to activate one or more second messengers that enhance transmitter release and thereby maintain LTP.

Unlike presynaptic terminals, which store transmitter in vesicles and release it at specialised release sites, the postsynaptic membranes lack any special release machinery, although dendro-dendritic synapses are well known and transmitter can be released from dendrites in the substantia nigra region of the brain. It therefore

seemed attractive to posit that the retrograde messenger may be a substance that rapidly diffuses out of the postsynaptic cell across the synaptic cleft and into the presynaptic terminal. By 1991 several group of researchers had obtained evidence that nitric oxide (NO) may be such a retrograde messenger (see figure 18). NO has a brief half-life (a few seconds). It is a rapidly diffusible gas produced by  $\text{Ca}^{2+}$ -calmodulin activated NO synthetase (Bredt and Snyder, 1992), even though there is a limited distribution of NO synthetase in the CNS.

Experiments suggest a role for NO in the hippocampal memory processes (Fin et al., 1995). Inhibiting the synthesis of NO in the postsynaptic neuron (Izquierdo and Medina, 1995) or absorbing NO in the extracellular space blocks the induction of LTP, whereas applying NO enhances transmitter release from presynaptic neurones.

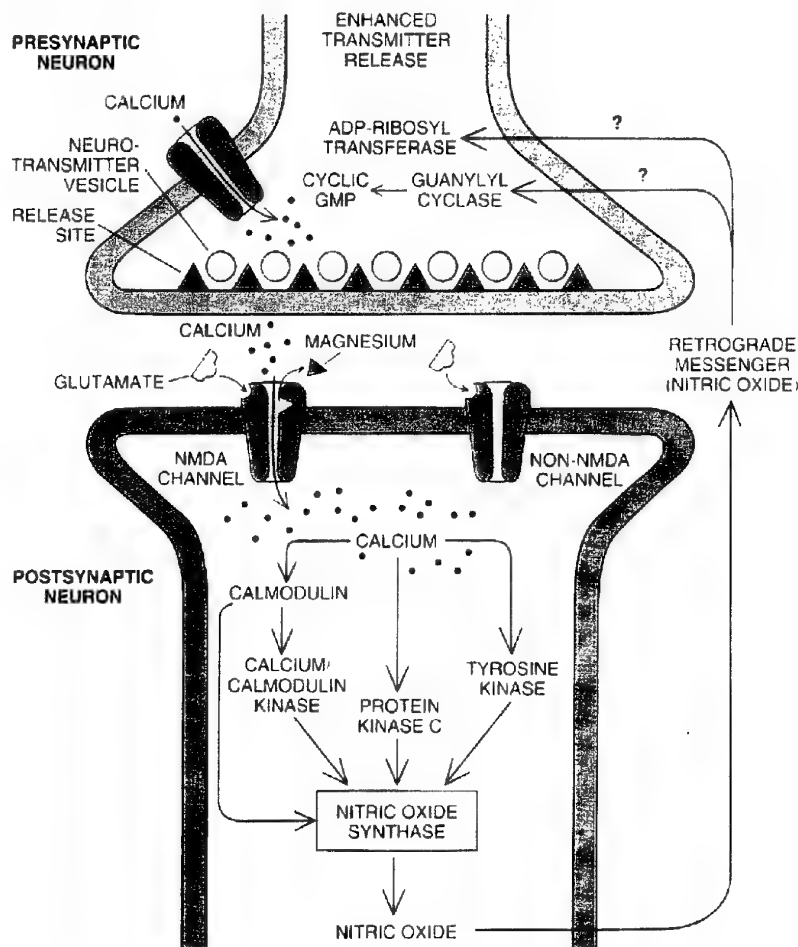


Figure 18. Some messengers believed to be involved in long-term potentiation. The flow of calcium in the postsynaptic cell triggers calcium-dependent kinases that lead to the induction of LTP. It is shown that the retrograde messenger, possibly nitric oxide, acts in the presynaptic terminal to enhance transmitter release, perhaps by activating guanylyl cyclase or ADP-ribosyl transferase. Some of these messengers are believed to also be involved in long-term desensitisation, or LTD, in cerebellar Purkinje cells.

It has been reported that NO produces LTP only if it is paired with activity in the presynaptic neurones, much as is the case in activity-dependent presynaptic facilitation in *Aplysia*. Presynaptic activity, and perhaps calcium influx, appears to be critical for NO to produce potentiation. These reports suggest LTP uses a combination of two independent, associative, synaptic learning mechanisms: a Hebbian NMDA receptor dependent mechanism and a non-Hebbian, activity-dependent, presynaptic facilitating mechanism. Activity dependence of presynaptic facilitation could be a way of ensuring that only specific presynaptic pathways, those that are active are potentiated. Any inactive presynaptic terminals would not be affected.

The second messenger, arachidonic acid, is generated from the degradation of membrane phospholipids by phospholipase A<sub>2</sub>, a calcium-dependent enzyme (Williams et al., 1989; Bliss et al., 1990). It has a longer half-life and it can thus modulate presynaptic action potentials, and is likely to have a wider diffusion range. Arachidonic acid can be produced by a variety of neurones in the CNS. Carbon monoxide (CO) has also been advocated as a possible retrograde messenger.

The effects of these retrograde messengers on presynaptic functions probably involve a modification of the enzymatic processes regulating neurotransmitter release. These messengers initiate changes at the synapse by switching on IEGs which then produce new cellular components for deposition at the synapse. It is believed that arachidonic acid acts by activating phosphorylation reactions in the presynaptic terminals that are linked to the regulation of transmitter release. Similarly, NO has been shown to stimulate the synthesis of cyclic GMP and to increase neurotransmitter release.

Figure 19 clearly summarises various biochemical processes associated with LTP.

If the retrograde facilitating substance in the hippocampus were able to diffuse widely, the facilitation would also occur at synapses onto other postsynaptic cells, as found in *Aplysia* (Hawkins and Kandel, 1990). Such a result has been observed in monolayer cultures of hippocampus by Bonhoeffer et al. (1989). They found that induction of LTP in any given cell in CA1 (by a Hebbian mechanism) leads to the expression of LTP in neighbouring postsynaptic cells through a non-Hebbian step in which the postsynaptic cell does not fire. A similar mechanism has also been found by Kossel et al. (1990).

Alternative to presynaptic enzymatic processes, the retrograde message could involve changes in the ionic constituent of the fluid in the synaptic cleft (e.g. an increase in Ca<sup>2+</sup> levels), or it could take a mechanical form, with the postsynaptic cell interacting with the presynaptic cell through a pull chain made up of extracellular connective molecules.

Laduron (1987a, 1987b) postulates that presynaptic terminals are receptive to neuromodulators released either as a retrograde messenger from the postsynaptic membrane, or from axo-axonic connections. More transmitter is released with repetition. To account for long term changes he proposes that the messenger neurotransmitters are packaged into vesicles along with their receptors (pinched off from the axon terminal) and transported back to the cell body by fast axonal (retrograde) transport. There, the occupied receptors influence the nucleus to

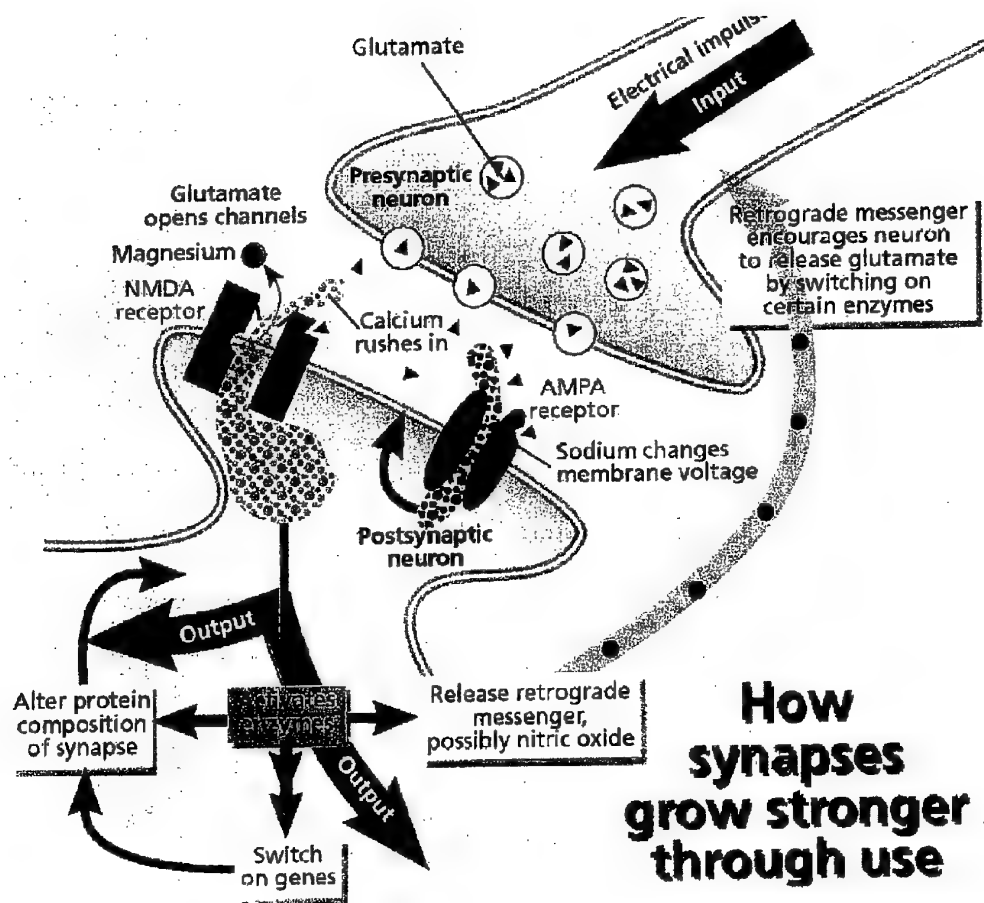


Figure 19. Simple representation of chains of biochemical events that induce LTP, and maintain it through an increase in the efficacy or strength of synapses.

transcribe different proteins, specifically ion channels. These would then be sent, by anterograde transport to the terminals, where the efficiency of the synapse would be enhanced by the structural modification, which thus becomes, in effect, the memory trace. This is shown in figure 20.

However, the half-time of the retrograde messenger substances, and the fact that they are not parcelled up into vesicles, suggests that they do not provide the means of satisfying Laduron's hypothesis.

### 7.3. Hippocampal LTP relationships to learning and memory

LTP is rapidly induced. It reaches steady-state in less than 10 minutes. LTP has been measured in hippocampal slices for periods in excess of 12 hours after it has been triggered. Once established, LTP can last for hours to several weeks in hippocampus *in vivo* (Staubli and Lynch, 1987), enduring enough to make it a likely candidate for the physical changes that underpin the formation of recent memories. LTP can be distinguished from less enduring forms of synaptic plasticity such as short-term potentiation (STP) and post-tetanic potentiation (PTP), which appear to be mediated by different cellular mechanisms (Bliss and Collingridge, 1993).

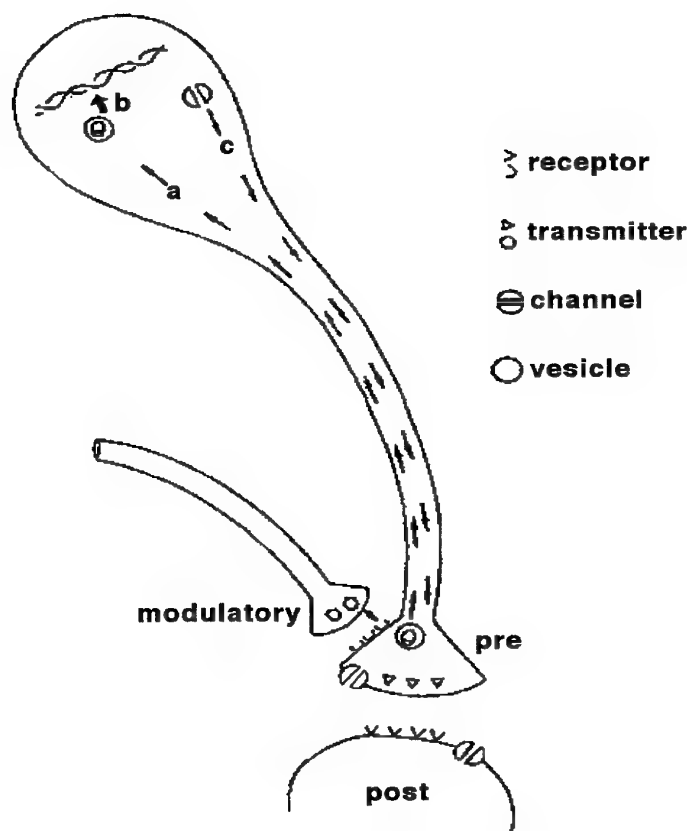


Figure 20. Long-term potentiation through regulation of gene function in a mechanism suggested by the work of Laduron (1987a, 1987b). (a) Neurotransmitters attached to their receptors are transported in vesicles to the cell body. (b) The occupied receptors then activate genes for protein synthesis. (c) Specifically, ion channels could be produced which, when inserted into the cell membrane, would modify the electrical activity of the neuron.

Perhaps the strongest evidence for a role of LTP in learning and memory comes from studies using pharmacological antagonists of the NMDA receptor. NMDA receptor antagonists impair learning when applied either systemically (Robinson et al., 1989; Shapiro and Caramanos, 1990), intracranially (Morris et al., 1986; Staubli et al., 1989; Kim et al., 1991), or locally to specific brain structure (Jerusalinsky et al., 1992; Young et al., 1994), but the performance of learned responses is not affected by NMDA receptor antagonists (Kim et al., 1991).

Richard Morris and his colleagues at the University of Edinburgh Medical School (Morris et al., 1986) found that the induction of LTP by tetanic stimulation *in vivo* was blocked when NMDA receptors in the hippocampus were blocked by a selective antagonist AP5, and the degree of blocking was dose-dependent. Morris then turned to the behavioural tests. He chose the well-known water-maze task, wherein a rat put into a vat of milky water must learn where the submerged platform is so that it could leave the vat. Learning the platform whereabouts and spatial learning in general is believed to require an intact hippocampus. Morris discovered that learning the water-maze task was indeed retarded by the application of AP5, and



moreover, the degree of retardation was dose-dependent. Could this disruption have been due to some general impairment of the brain? This is unlikely, argues Morris, because the rats were able to perform another task, i.e. choosing between two raised platforms in the tank on the basis of visual cues with ease. This suggests that their motivation, their senses and so on were all intact. These experiments suggest that NMDA receptor mechanisms in the hippocampus, and Hebbian type LTP, are involved in spatial learning. Specifically, it has lately been shown that LTP in the area CA1, but not in cortical input to the dentate gyrus, seems to be required for spatial learning (Nosten-Bertrand et al., 1996)

Similarly, antagonists of the glutamate AMPA (Jerusalinsky et al., 1992) and metabotropic (Riedel et al., 1994) receptors have also been shown to impair learning. In addition, pharmacological blockade of AMPA receptors abolishes the expression of learned responses in a number of paradigms (Bianchin et al., 1993; Kim et al., 1993; Izquierdo and Medina, 1995), and drugs that enhance AMPA receptor function improve learning and memory (Granger et al., 1993; Staubli et al., 1994). Further evidence for a postsynaptic AMPA receptor role in learning and memory comes from studies indicating that both LTP and classical conditioning are accompanied by similar changes in the binding properties of AMPA receptors in the hippocampus (Tocco et al., 1992; Cammarota et al., 1995).

There are other reasons why LTP has become so central to theories about learning. Firstly, it acts in an impeccably "Hebbian" manner, only taking place at pre- and post-synaptic synapses connecting neurones that are both active at the same time. This is pairing between presynaptic activity and postsynaptic depolarisation (Brown et al., 1990). Secondly, it behaves like a cellular mimic of classical (*Pavlovian*) conditioning (Barrionuevo and Brown, 1983; Sastry et al., 1986). The associative property of LTP is perhaps one of its most important because it can be used to explain various forms of learning. During classical conditioning an initially neutral conditioned stimulus (CS; i.e., the weak pathway) comes to elicit a conditioned response (CR) similar to the unconditioned response (UR) elicited by an initially non-neutral unconditioned stimulus (US; i.e. the strong pathway). In this example, depolarisation generated by the stimulation of the strong US pathway promotes NMDA receptor activation and LTP in the weaker CS pathway, which consequently becomes a potentiated CR pathway (Kelso et al., 1986). As a result, LTP shows *specificity*: it is restricted in its action to the pathway that is stimulated. It also shows cooperativity (Bliss and Collingridge, 1993). Diamond and Rose (1994), however, believe that there are flaws in the extrapolation that associative LTP is a substrate for classical conditioning from both physiological and cognitive perspectives, and propose an alternative hypothesis in which the relevance of the associative LTP findings to hippocampal function is considered in a broader behavioural context, which encompasses classical conditioning. There are experimental results to suggest that behavioural events due to conditioned and unconditioned stimuli can exert bidirectional control of synaptic strength of entorhinal cortex inputs to the dentate gyrus, and that potentiation or depression of synaptic modification is at least partially determined by the temporal relationship between these events (Doyere et al., 1995).

Prior to stabilisation, LTP formation can be disrupted by a variety of manipulations such as hypoxia (Arai et al., 1990), electroconvulsive shock or seizure activity (Massicotte et al., 1991), trains of low frequency stimuli (Fujii et al, 1991), and cooling

shocks (Muller, 1994). The vulnerability of LTP to disruption suggest a possible basis for the consolidation period frequently observed in behavioural studies of learning and memory (Kim and Fanselow, 1992). Also, behavioural manipulations such as stress that impair LTP induction (Diamond et al., 1990) produce impairments in hippocampus-dependent spatial learning (Shors and Dryver, 1992). Moreover, studies using electrical stimulation to saturate LTP before training show that LTP saturation can have an impact on some forms of learning (Berger, 1984).

There is evidence that age-dependent impairment of spatial learning is associated with reduced hippocampal CA1  $\text{Ca}^{2+}$ -induced long-term potentiation (Barnes, 1979; Diana et al., 1995), and changes in glutamate receptor binding (Pelleymounter et al., 1990; Clark et al., 1992).

Further support for a LTP role in memory is indicated by the high correspondence between optimal LTP induction conditions and endogenous patterns of neural activity that accompany learning (Larson et al., 1986). In the CA1 region of the rat hippocampus, two quite different population effects have been observed (Buzsaki, 1989). One characteristic pattern, sharp waves, occur irregularly between 0.02 and 3 Hz. These waveforms are present during rest and consolidation as well as during deep sleep. Their amplitude is much higher than that of the other pattern known as theta waves (Buzsaki, 1986). Theta rhythm is regular between 4-12 Hz, and is low amplitude. Specifically, LTP is induced optimally by afferent stimulation that is patterned at theta frequency (Larson and Lynch, 1986). This is a frequency band that dominates the hippocampal EEG during information-gathering behaviours, such as exploration and experiencing in rats (Vanderwolf, 1969), and is also generated during the REM stage of sleep. The relationship between theta rhythm and learning and memory has been known for decades (Klemm, 1976; Landfield, 1976).

GABA<sub>B</sub> receptors can regulate LTP induction by modulating the level of inhibition. GABA<sub>B</sub> receptor-mediated fading of inhibition enhances both LTP induction and the spread of neural activity (Mott and Lewis, 1994). Theta frequency stimulation is optimal for LTP induction because it facilitates GABA<sub>B</sub> autoreceptor-mediated depression of inhibitory interneurons, thereby opening a time window for the postsynaptic target to sufficiently depolarise and activate NMDA receptors (Mott and Lewis, 1991). Thus, the hippocampal network seems to be particularly fine-tuned to exhibit maximal synaptic plasticity when global activity emerges in the theta range, a phenomenon that occurs during learning. There are reports of LTP-like changes in hippocampal electrophysiology during associative learning (Roman et al., 1987; Skelton et al., 1987) and exploration (Sharp et al., 1989; Green et al., 1990). However, a recent report by Moser et al. (1993) indicates that the changes in brain temperature that accompany exploration may be responsible for the increases in hippocampal responses. The relevance to memory of such exploration-related increases in hippocampal responses may therefore be questionable (Eichenbaum and Otto, 1993).

Inasmuch as sharp waves are strong relative to theta waves, involve synchrony of activations across a number of cells, and occur during a "quiet" phase following exploratory behaviour, these sharp waves are not implausible candidates for the natural counterpart of the experimental conditions leading to LTP (Buzsaki 1989; Buzsaki and Gage, 1991).

### 7.3.1. A two stage learning hypothesis

Buzsaki proposes a learning hypothesis, where in stage one, during theta rhythm, information is transferred from the entorhinal to CA3 area by fast-firing granule cells which converge on the CA3 pyramidal cells so as to produce weak and transient heterosynaptic potentiation. During this phase, the pyramidal cells also receive rhythmic inhibition originating from the septum. The pattern of potentiation in CA3 cells is a function of the pattern of input from cortical structures, and creates a temporary store of information. Because CA3 pyramidal output is silenced during this phase, CA1 cells are not activated by the CA3 pyramidal cells. Once exploratory behaviour has ceased, the CA3 cells are released from septal inhibition and can then discharge in bursts, the most recently and hence most strongly excited ones first. The extensive pattern of recurrent collaterals connecting a cell to itself, and to other pyramidal cells in the region, means that the network self-organises into complex patterns of activity. Excitation is spread to less active (earlier stimulated) cells by recurrent collaterals. These cells then also discharge. The bursts from the CA3 pyramidal cells in effect “teach” the CA1 cells, the most recent “events” being the first and most strongly signalled. The CA1 cells in consequence undergo long-term modification. A more permanent trace may also be left on some CA3 cells, as well as some cells in entorhinal cortex by way of feedback from CA1.

### 7.4. Relationship between development and structural modifications involved in learning and memory

Experiments in both the sea hare *Aplysia* and mammals indicate that explicit and implicit memory storage proceed in stages. Storage of initial information, a type of short term memory, lasts minutes to hours and involves changes in the strength of existing synaptic connections (by means of second-messenger-mediated modifications). The long term changes that persist for weeks and months are stored at the same site but, as detailed in the section on plasticity, may involve activation of genes, the expression of new proteins, and growth of new connections, such as an increase in the number of presynaptic terminals. Researchers have found that in *Aplysia* artificial electrical impulses which produce a form of long-term memory also cause synapse-like structures to grow on the nerve fibres. If long-term memory leads to anatomical changes, does that imply our brains are constantly changing anatomically as we learn and as we forget? There is now reason to believe that the fine-tuning of connections during late stages of development may require an activity-dependent associative synaptic mechanism, perhaps similar to LTP. If that is also true on the molecular level, if learning shares common molecular mechanisms with aspects of development and growth, the study of learning may help connect cognitive psychology to the molecular biology of the organisms in a more general way.

### 7.5. Pharmacological modulation of learning and memory

An understanding of the molecular and cellular mechanisms underlying various forms of synaptic plasticity, such as LTP, provides a framework to evaluate the effects of specific drugs on learning and memory. For example, in view of the role of cholinergic neurones in the generation of the theta rhythm (Bland, 1986), the effects of drugs interacting with cholinergic neurotransmitter systems can now be interpreted in relation to hippocampal theta rhythm and LTP induction (Hasselmo

and Barkai, 1995). Similarly, the effects on learning and memory of drugs acting on GABA receptors can be accounted for on the basis of their effects on LTP induction mechanisms (Baudry and Massicotte, 1992). Indeed, blockade of GABA<sub>B</sub>, as with GABA<sub>A</sub> receptor-mediated IPSPs can facilitate the induction of LTP, because elimination of their hyperpolarising influence enhances the expression of the NMDA receptor-mediated conductance (Davies et al., 1991). In particular, memory and LTP are reported to be blocked early on by GABA<sub>A</sub>-receptor agonists, and enhanced by GABA<sub>A</sub>-receptor antagonists (Izquierdo and Medina, 1995). Some phosphonous acid analogues of GABA are capable of crossing the blood-brain barrier after oral administration. Such GABA<sub>B</sub>-receptor antagonists, through facilitating the induction of long-term potentiation *in vivo* and *in vitro*, can produce cognitive enhancing effects (Froestl et al., 1995). Indeed, it has recently been reported that dehydroepiandrosterone sulfate, which as a neurosteroid acts on GABA receptors, produced a significant increase in LTP in relation to baseline values (Yoo et al., 1996). It has also been suggested that sex steroid hormones influence neural plasticity, neuronal activity and possibly learning and memory (Priest and Pfaff, 1995). Moreover, it has been found that the induction of LTP *in vivo* is suppressed by low doses of ethanol, which is believed to act on GABA<sub>A</sub>-receptors. This effect may underlie impairment of learning and memory by ethanol (Givens and McMahon, 1995).

Opioids in the hippocampus could play an important role in learning and memory by mediating inhibitory responses through kappa and mu receptors. In fact, opioids seem to inhibit GABA release as, in some animals such as sheep and dog, opioids almost cause seizure activity. Mossy fibres constitute the principal source of dynorphin and enkephalin in the hippocampus (Salin et al., 1995).

Attempts have been made to develop new pharmacological tools that would be specific and selective for bio-chemical systems involved in learning. In this regard, several attempts have been made to develop cognitive enhancers based on the properties of synaptic plasticity mechanisms. A glycine analogue, D-cycloserine (an allosteric modulator of the NMDA receptor), has been reported to reverse the amnestic effects of scopolamine (a cholinergic antagonist) in rats (Fishkin et al., 1993), and to facilitate learning in rabbits (Thompson et al., 1992). Another approach to produce cognitive enhancers would be to develop compounds that modulate the properties of AMPA receptors. For example, phosphatidylserine, a phospholipid which increases the affinity of AMPA receptors for agonists (Baudry et al., 1991), has been reported to improve cognitive impairments associated with aging (Zanotti et al., 1984; Corwin et al., 1985). This suggests that agents capable of allosteric modifications of AMPA receptors could be used as cognitive enhancers (Granger et al., 1993; Staubli et al., 1994). Looking beyond postsynaptic receptors, a better understanding of the enzymatic cascades involved in LTP might provide more selective ways of increasing synaptic efficacy.

## 8. Decreasing Synaptic Strength

Assuming that there is a mechanism, such as LTP, for strengthening connections between synapses, then to avoid saturation (meaning that all synapses do not end up at their maximum strength), some counterpart mechanisms probably exist to *decrease* synaptic strengths. In the absence of repetition, some connections may gradually decay over time, with the result that information is lost. Some of such processes might correlate with gradual forgetting on the psychological level. Weakening of the connections between synapses should, however, not be automatically identified with the psychological phenomenon of forgetting. Reduction in synaptic strength under specific presynaptic-postsynaptic conditions could well be an indispensable component of learning new information or, alternatively, it could be a part of sloughing off the irrelevant.

As the flip side of LTP, *long-term depression* (LTD), as a complementary inhibiting mechanism has been sought at the conventional LTP sites. LTD also provides a means for regulating the strength of synaptic connections in the mammalian brain. Two broad classes have been postulated, and there is some evidence for both. The first class is *heterosynaptic* LTD, which means that the responsivity of the whole cell is downregulated, equivalent in its consequence to changing the gain of the cell. The second class is *homosynaptic* LTD, wherein responsivity is damped at the very synapse manipulated, leaving other (unmanipulated) synapses on the same cell undamped. In both cases, a postsynaptic structure hitherto potentiated loses that potentiation in exchange for a depressed response to the presynaptic stimulus. These forms of LTD, as well as various forms of LTP, are shown in figure 21.

Heterosynaptic LTD is conjectured to have a role in normalisation, that is, in adjusting cells so that they are not saturated by LTP modifications. Homosynaptic LTD may be more selective and, thus, may be speculated to have a role in culling out low-grade or "don't-care" information.

Stanton and Sejnowski (1989) investigated whether there was an associative form of LTD in the hippocampus. They found that when a weak, test stimulus to one set of schaffer collateral inputs was applied out of phase with a strong, conditioning stimulus to an independent set of inputs, LTD was produced in the test stimulus pathway. The depression required the out-of-phase pairing of test and conditioning stimuli. As the out-of-phase test impulse arrived at a time when the postsynaptic cell was hyperpolarised due to an inhibitory GABAergic postsynaptic potential, Stanton and Sejnowski produced what appears to be homosynaptic LTD in a CA1 pyramidal cell from a slice preparation. First, LTP was produced in the standard way by high-frequency stimulation of the Schaffer pathway. In the next phase, current injected into the postsynaptic cell was manipulated so that it negatively correlated with presynaptic activation. Accordingly, when the presynaptic cell was active, the postsynaptic cell was artificially hyperpolarised and hence not allowed to respond. This depression is shown in figure 16.

### 8.1. Long-term depression in the cerebellum

Long-term depression (LTD) in cerebellar cortex is a widely studied form of synaptic plasticity in the mammalian brain. Cerebellar LTD has long been proposed as a

mechanism for various forms of motor learning mediated by the cerebellum. Its induction mechanisms and properties are briefly discussed below.

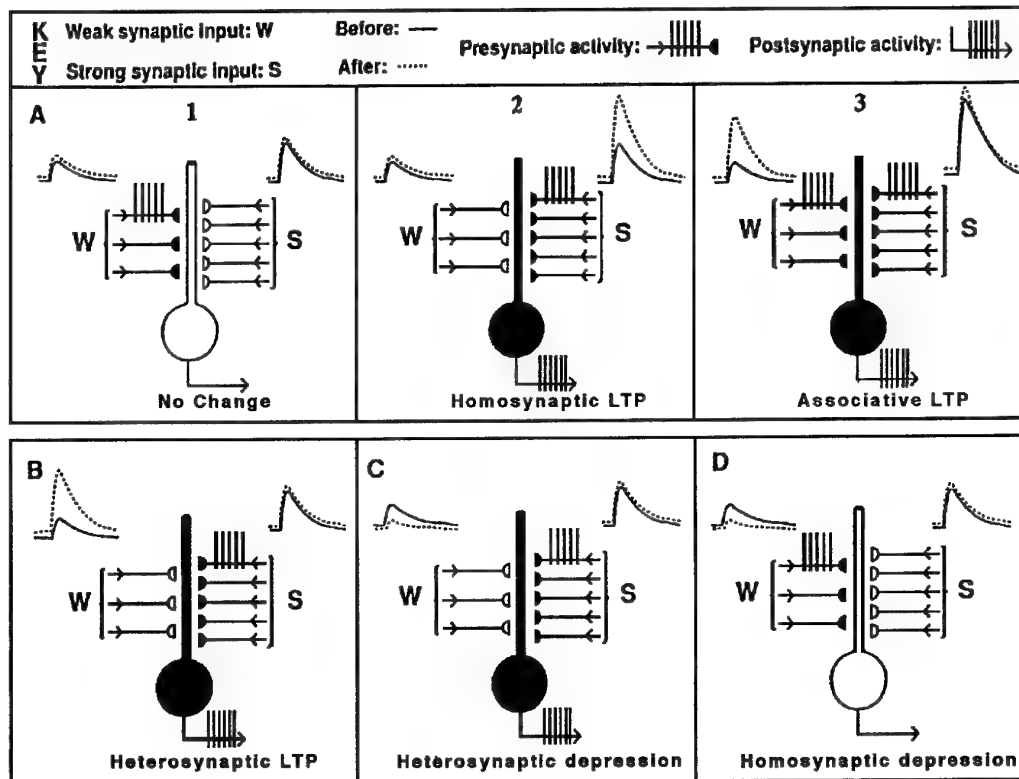


Figure 21. Use-dependent synaptic changes. Each neuron is shown to receive two sets of synaptic inputs. The waveforms above each input illustrate schematically the excitatory postsynaptic potential produced by a single stimulation of that input before (solid curve) and after (broken curve) tetanic stimulation of one or both inputs. Filled elements indicate activity during the tetanic stimulation (from Brown et al., 1990).

### 8.1.1. Mechanisms of cerebellar LTD induction

LTD in the cerebellar cortex can be induced either by pairing low-frequency activity (1-4 Hz for several minutes) in parallel fibres (PFs) of the granule cells and climbing fibres (CFs) arising from the inferior olive, two excitatory afferent pathways that converge on cerebellar cortical Purkinje cells (Ito, 1989), or by pairing PF activity with direct Purkinje cell hyperpolarisation (Crepel and Jaillard, 1991). Whereas a single Purkinje cell receives inputs from up to 80000 parallel fibres, it is innervated by only one climbing fibre. The Purkinje cells provide the only output of the cerebellar cortex. The timing of PF and CF stimulation is critical as optimal LTD occurs when PF and CF activation are 250 ms apart (Maren and Baudry, 1995). Following several pairing of PF and CF stimulation, synaptic responses in the PF pathway exhibit a marked and enduring depression. As in the hippocampus, fast excitatory synaptic transmission at both PF and CF synapses is mediated primarily by postsynaptic AMPA receptors (Perkel et al., 1990). However unlike LTP induction, the critical events in LTD induction involve the coupling of a potent  $\text{Ca}^{2+}$

signal generated by CF discharge with activation of mGluRs at parallel fibre-Purkinje cell synapses (Maren and Baudry, 1995). Cerebellar LTD does not involve NMDA receptors, nor does it seem to require GABA-mediated inhibitory inputs, since it is enhanced, not suppressed, by picrotoxin (Sakurai, 1987). An increase in intracellular  $\text{Ca}^{2+}$  in postsynaptic Purkinje cells is required for cerebellar LTD (Sakurai, 1988). This is because  $\text{Ca}^{2+}$  is an intracellular mediator of the climbing fibre LTD induction, and intracellular injection of the  $\text{Ca}^{2+}$  chelator EGTA into a Purkinje cell blocks the induction of LTD (Sakurai, 1990). This elevation in intracellular  $\text{Ca}^{2+}$  is probably mediated by both voltage-gated  $\text{Ca}^{2+}$  channels activated by CF depolarisation, and the liberation of intracellular  $\text{Ca}^{2+}$  stores by a metabotropic receptor-mediated second messenger cascade (Okamoto and Sekiguchi, 1991). It may be that simultaneous activation of glutamate AMPA and metabotropic receptors are required for climbing fibre-induced long-term depression. The modification that expresses LTD at PF synapses appears to be a sustained desensitisation of ionotropic AMPA receptor responses (Linden et al., 1991).

Therefore, the final common pathway for the induction and expression of both hippocampal LTP and cerebellar LTD is an elevation of intracellular  $\text{Ca}^{2+}$ , an activation of enzymatic cascades, and a modification of postsynaptic AMPA and metabotropic sub-types of glutamate receptors. Unlike LTP, however, the rise in  $\text{Ca}^{2+}$  in Purkinje cell dendrites is thought not to be through the NMDA-type channels.

How does the rise in intracellular  $\text{Ca}^{2+}$  leads to LTD? Recent evidence implicates the production of cGMP through the NO cascade (Ito and Karachot, 1990; Shibuki and Okasa, 1991). According to this hypothesis, the rise in intracellular  $\text{Ca}^{2+}$  activates the  $\text{Ca}^{2+}$ -calmodulin-dependent enzyme, NO synthetase (Bredt and Snyder, 1990). NO then activates a soluble form of guanylate cyclase leading to production of cGMP. The links between these messengers are shown in figure 18. Shibuki and Okasa (1991) detected the release of NO in response to white matter stimulation in cerebellar slices during induction of LTD, and found that several inhibitors of NO production also blocked induction of LTD. Ito and Karachot (1990) found that LTD could also be inhibited by inhibiting certain GTP-binding proteins (Gi and Go), and by inhibitor of the cGMP-dependent protein kinase.

A similar cascade of events might also be responsible for LTD induction in other brain structures. Like cerebellar LTD, neocortical LTD induction does not require NMDA receptor activation (Artola et al., 1990; Hirsch and Crepel, 1991). However, LTD induction in the hippocampus, like LTP induction, does require NMDA receptor activation (Dudek and Bear, 1992; Mulkey and Malenka, 1992).

### 8.1.2. Properties of cerebellar LTD

Cerebellar LTD shares many memory-like properties that hippocampal LTP exhibits. LTD is long-lasting. It has been observed to last for hours in *in vivo* preparations (Ito, 1989). LTD is specific to stimulated synapses i.e., PFs that are not paired with CF stimulation do not show LTD. LTD induction obeys Hebbian rules as strong postsynaptic depolarisation generated by CFs is combined with presynaptic neurotransmitter release at PF-Purkinje cell synapses. The Hebbian nature of cerebellar LTD also provides for associativity.

One potential problem for a role for cerebellar LTD in learning is the lack of correspondence between optimal LTD induction parameters and optimal learning parameters in cerebellum-dependent tasks. Classical eye-blink conditioning in rabbits may depend on cerebellar LTD (Thompson, 1990). In this paradigm, an auditory CS precedes a corneal air puff US. After several pairing, the CS comes to elicit an eyeblink CR. Cerebellar cortical damage severely impairs both the acquisition and retention of this learned response as CS and US information are conveyed to cerebellar cortex by PFs and CFs, respectively. A 250 ms CS-US interval produces robust LTD in the cerebellum (Maren and Baudry, 1995). It has been reported that NO synthesis inhibitors, which impair cerebellar LTD induction, impair eyeblink conditioning in rabbits (Chapman et al., 1992).

Both LTP and LTD have been reported in several other brain structures including amygdala (Chapman et al., 1990; Clugnet and LeDoux, 1990), and Neocortex (Artola and Singer, 1993; Hirsch and Crepel, 1990).



## 9. Long-Term Synaptic Plasticity in Artificial Neuronal Networks

In order to model hippocampal and cerebellar functions, artificial neuronal networks have been designed with synaptic plasticity rules similar to those found in hippocampal LTP and cerebellar LTD. Although these models are still in their infancy, they have already proved to be powerful tools for understanding the computational and "cognitive" properties of certain types of network designs and rules.

Networks with plasticity rules derived from hippocampal LTP have been shown to produce an optimal classification of input signals, and to have a very large storage capacity (Ambros-Ingerson et al., 1990; Granger and Lynch, 1991; Granger et al., 1994). Similarly, networks designed according to cerebellar circuitry and plasticity exhibit properties of complex motor learning and adaptation (Chapeau-Blondeau and Chauvet, 1991).

The next generation of artificial neuronal networks will have to incorporate more biological features in order to reproduce more sophisticated performance of the neural networks they intend to simulate. In particular, more detailed information concerning the mechanisms of receptor activation, receptor regulation and second messenger signalling will have to be incorporated to understand the consequences of cellular responses that are measured in seconds and minutes instead of milliseconds. There is no doubt this kind of consistent updating of neuronal responses is involved in the continuous nature of information processing and storage.

Edmund Rolls (1989) discerned a resemblance between hippocampal anatomy and the associative nets of Hopfield and Kohonen. He suggests that the CA3 region is a recurrent net, where the mossy fibres provide a coarsely specified input, whereas the more dense and direct perforant input determines the finer discriminations, and the collaterals allow both for upgrading noisy patterns and completing partial patterns (see figure 22). According to Rolls proposal, the CA3 region is a structure for recognition memory. In rat each CA3 neurone receives inputs from 12000 other CA3 neurones, exactly the kind of pattern one would expect, says Rolls, if the area worked as an autoassociation memory. The CA1 region, as recipient of CA3 signals, Rolls sees as a matrix for competitive learning, where the function is to perform further classification on what it gets from a set of CA3 pyramidal cells, yielding a more general, or as he says "economical" classification of world events. Since Rolls does not give a specific example of what that would mean, or of the contrast between CA1 and CA3 representations, it is not clear what sort of representation further classification by the CA1s produces, or why, given its Rollisian function, CA1 learning should be competitive. Rolls' hypothesis remains at a very abstract level of explanation. What is missing from the account is the differential physiology of hippocampal cells and what, given the anatomy, could be its significance in learning new things.

Roger Traub and his colleagues have explored models of CA3 region as it behaves in slices (Traub et al, 1989; Traub and Dingledine, 1990). The Traub models of slice data have distinctive cell populations corresponding to excitatory pyramidal cells (9000), and two kinds of inhibitory cells (450 of each). The models incorporated a great many biophysical and physiological properties of cells, such as fast and slow GABA

receptors, channel types, and time constants, as well as the details of synaptic distribution, and patterns of connectivity between the pyramidal cells, mossy fibres and inhibitory cells. One question asked of the model by Traub and Dingledine (1990) was related to the generation of *in vitro* synchronised bursts, presumably corresponding to the sharp waves seen *in vivo*. They found that in the model synchronous bursts were preceded by a barrage of EPSPs, caused by granule cell action potentials. In the model, while spontaneous EPSPs in CA3 pyramidal cells were necessary to the initiation of the bursting phase, recurrent collaterals were necessary for synchronisation of the bursts.

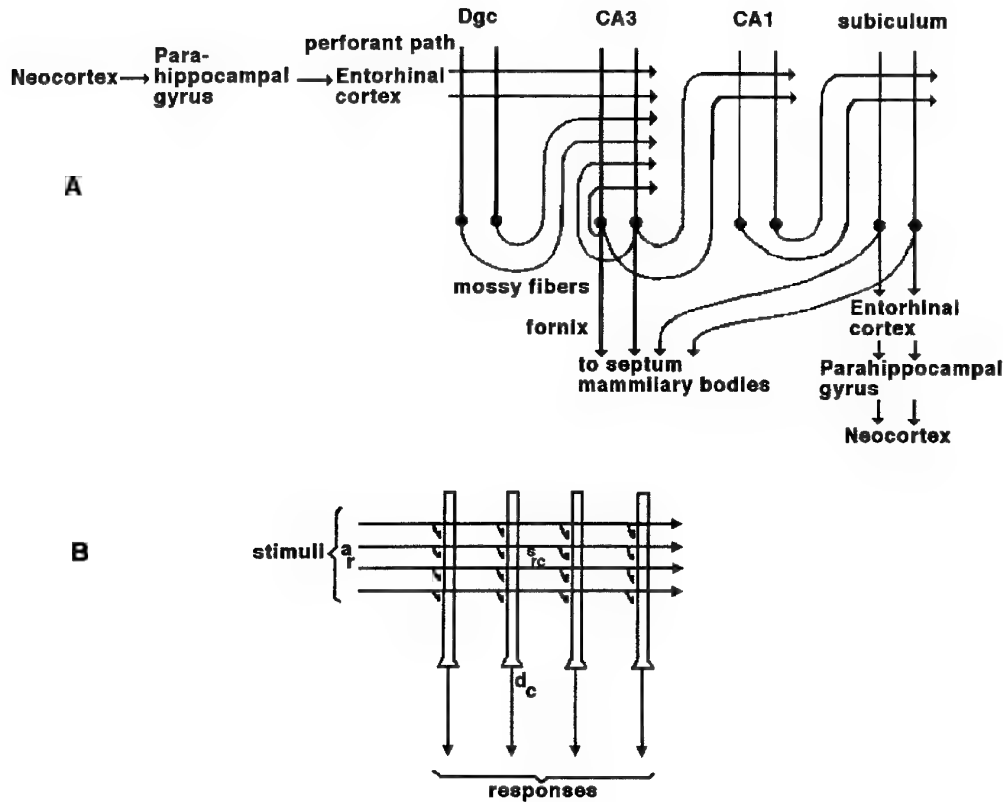


Figure 22. (A) Schematic representation of the connections of the hippocampus and its projections to and from the cerebral cortex. (B) Matrix for competitive learning in which the input stimuli are presented along the rows of the input axons ( $a_i$ ), which make modifiable synapses ( $S_{rc}$ ) with the dendrites of the output neurones forming the columns ( $d_c$ ) of the matrix. A net with this architecture is rather like the neural architecture of feedforward Schaffer collaterals from CA3 to CA1 pyramidal cells (from Rolls, 1989).

## 10. Conclusions

From the analysis on mechanisms and properties of long-term synaptic plasticity, an explanation for memory storage and recall may emerge that once all the synapses have put Hebbian rule into effect, the memory has been stored. Neurones that were once active together are now linked by stronger synapses; during recall they will tend to rouse one another and help to recreate the original pattern.

Multidisciplinary studies bridging behaviour, systems neurophysiology, receptor biochemistry, and molecular genetics will be the wave of the future to enhance the connection between LTP and memory. For example, a multidisciplinary approach to bridge hippocampal glutamate receptor binding, LTP, and learning is demonstrated by the finding that acute water deprivation increases hippocampal AMPA receptor binding, elevates hippocampal LTP expression and theta rhythm (Maren et al., 1994b), and markedly facilitates the acquisition of Pavlovian fear conditioning in rats (Maren et al., 1994a; Maren et al., 1994b)

There is increasing research in the area of gene knockout technology for the analysis of learning and memory, and neural development (e.g. Tonegawa et al., 1995). In view of recent reports of specific IEG induction following LTP induction (Schreiber et al., 1991) and learning (Campeau et al., 1991; Pezzone et al., 1992), IEG knockouts may be a profitable avenue for future studies of the relationship of synaptic plasticity to learning and memory.

- (a) Elucidation of the molecular and cellular mechanisms of LTP has now provided an explanation for the relationship between global events occurring during information acquisition and processing, and local storage of information

The two stage hypothesis by Buzsaki which was outlined earlier is well rooted in data from cellular and area levels, and it renders coherent some otherwise puzzling data. Importantly, it opens up a range of testable sub-hypotheses and predictions. One direct prediction, for example, is that the retention of a task will be significantly better if followed by a sleep episode than if followed by continuing intense activity, since sharp waves are especially manifest during deep sleep.

- (b) Understanding the cellular and molecular mechanisms of LTP has provided not only new interpretation for results of pharmacological studies concerning memory, but also new tools such as receptor binding techniques to probe neural systems for LTP-related changes and new pharmacological compounds to analyse the role for LTP in information processing and storage. It is now possible to make some testable predictions concerning the potential effects of drugs on memory processes.
- (c) Computer simulations of biologically relevant neural networks have begun to incorporate biologically relevant parameters based on LTP induction rules (e.g. Willshaw and Buckingham, 1990; Ekeberg et al., 1991; Granger et al., 1994). These models have the potential to become powerful tools to link neurobiology and cognitive sciences. Such neural networks will have many applications. For example, in theory, a fully fledged cellular network of the

type proposed by Edmund Rolls in 1989, an autoassociation memory, could hold many memories simultaneously, with each synapse participating in several memories and each memory being "encoded" by several synapses. Its power of recall would be spectacular. If prompted with only a small fragment of a memory, its synapses would ensure that it regenerates that memory in its entirety.

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**Mechanisms and properties of long-term synaptic plasticity in the brain:  
Relationships to learning and memory**

*A. Hashem-Sakhtsari*

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19. ABSTRACT  Functional and structural changes in synapses, specific regions for communication between nerve cells, are thought to be the basis for storing information, and modulating neuronal behaviour. This continuous remodelling is defined as synaptic plasticity. The process of learning involves stable changes in synaptic efficacy. Long-term potentiation in the hippocampus and long-term depression in the cerebellum are two forms of long-lasting synaptic plasticity that currently serve as our primary experimental models of learning and memory formation. In recent years, there have been considerable advances in understanding the cellular and molecular mechanisms of these forms of synaptic plasticity. This report presents an overview of these developments, considers the relationship of long-term synaptic plasticity mechanisms to learning and memory in view of these developments, and suggests future directions for research in this rapidly growing area of neuroscience. Amongst these proposals, any artificial neuronal network model should contain elements that imitate the use-dependent increase (or decrease) of synaptic efficiency.					